In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-0143V
Filed: December 15, 2023

VALERIA HERNANDEZ, as the legal representative of her minor daughter, S.H.

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Curtis R. Webb, Monmouth, OR, for petitioner.
Alexa Roggenkamp, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On January 30, 2017, petitioner filed a petition on behalf of her minor daughter ("S.H.") under the National Childhood Vaccine Injury Act ("Vaccine Act"), 42 U.S.C. § 300aa-10, *et seq.* (2018).[2] (ECF No. 1.) Petitioner alleged that S.H. suffered seizures leading to epilepsy caused by her May 22, 2015 Pediarix (consisting of diphtheria-tetanus-accellular pertussis ("DTaP"); hepatitis B; and polio vaccines), haemophilus influenzae B ("HIB"), pneumococcal conjugate ("Prevnar 13"), and rotavirus vaccinations. (*Id.*) For the reasons discussed below, I conclude that petitioner is *not* entitled to compensation.

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period also specified in the Table. If so, causation is presumed and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In these cases, the presumptions available under the Vaccine Injury Table are inoperative. Instead, the petitioner bears the burden of showing by preponderant evidence that the vaccine recipient's injury was actually caused by the alleged vaccination, often referred to as "causation-in-fact". § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii); *see also Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). In this case, petitioner alleges S.H. suffered seizures and epilepsy, which are not Table injuries. Nor does petitioner otherwise allege that these injuries constitute manifestations of any Table injury. Accordingly, petitioner must satisfy the burden of proof for "causation-in-fact."

Under the causation-in-fact standard, the petitioner must show that it is "more probable than not" that the alleged vaccination was the cause of the alleged injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury, but must establish that the vaccination was at least a "substantial factor" and "but for" cause of the condition. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1). The petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" and this proof must be supported by "reputable medical or scientific explanation, *i.e*., evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992).

In what has become the predominant framing of this burden of proof, the *Althen* court described the causation-in-fact standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

Generally, respondent bears the burden of demonstrating the presence of any alternative cause by preponderant evidence only if petitioner satisfies her *prima facie* burden. § 300aa-13(a)(1)(B); *Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1150 (Fed. Cir. 2007). Respondent may also present evidence relating to an alternative cause to demonstrate the inadequacy of petitioner's evidence supporting her case in chief, but petitioner does not bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case under *Althen*. *de Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352-53 (Fed. Cir. 2008); *Walther*, 485 F.3d at 1150.

II. Procedural History

Petitioner filed her petition for compensation on January 30, 2017. (ECF No. 1.) Petitioner also filed an affidavit and several medical records. (Exs. 1-6.) The following day, this case was assigned to Special Master Millman, who subsequently ordered petitioner to file an expert report supporting her claim. (ECF No. 4.) Special Master Millman issued an order setting out a series of issues, including whether petitioner had satisfied the six-month severity requirement and whether S.H.'s parents may have misinterpreted her spells based on their identification of events that were not recorded as seizures during the EEGs. (ECF No. 7.) She ordered petitioner to file an expert report. (ECF No. 10.)

Petitioner filed an expert report from Dr. Marcel Kinsbourne with accompanying literature in October of 2017. (ECF No. 13-15; Exs. 7-23.) In January of 2018, respondent filed his Rule 4 report, recommending against compensation, along with an expert report by Dr. Gregory Holmes and supporting medical literature. (ECF Nos. 18-21; Exs. A-B.) Petitioner filed a supplemental expert report and supporting literature

from Dr. Kinsbourne the following May. (ECF No. 25, 27; Exs. 24-26.) Respondent filed a supplemental expert report from Dr. Holmes in July of 2018. (ECF No. 29; Ex. C.)

Thereafter, Special Master Millman issued an order queuing the case for an entitlement hearing following her retirement. (ECF No. 30.) This case was reassigned to my docket in June of 2019. (ECF Nos. 32-33.) I ordered petitioner to file updated medical records, which were filed in March of 2020. (ECF Nos. 34, 36; Ex. 27.) I held a follow up status conference with the parties in April of 2020. (ECF No. 37.) I explained that, based on my review of the updated medical records, it appeared that the question of the statutory severity requirement would likely turn on S.H.'s treatment with phenobarbital. (*Id.* at 1.) I also encouraged the parties to review a separate decision I issued in *Kottenstette v. Secretary of Health & Human Services*, No. 15-1016V, 2020 WL 4197301 (Fed. Cl. Spec. Mstr. June 2, 2020).[3] (ECF No. 38.)

An entitlement hearing was set in this case to be held in August of 2022. (ECF No. 44.) In the interim, petitioner filed a further supplemental report by Dr. Kinsbourne and respondent filed a responsive report by Dr. Holmes along with an additional report by Dr. Herman Staats. (ECF Nos. 46, 49, 52-55, 57-61; Exs. 28-44, D-E.) Petitioner filed her final expert report from Dr. Kinsbourne on February 28, 2022, and respondent filed his final reports on May 6, 2022. (ECF Nos. 65, 71; Exs. 45-53; Exs. G-H.)

An entitlement hearing was held on August 16, 2022. (*See* Transcript of Proceedings ("Tr.") at ECF No. 86.) Petitioner, Dr. Kinsbourne, Dr. Holmes, and Dr. Staats testified. This case is now ripe for a ruling on entitlement. (*See* Tr. 161 (counsel agreeing record is closed).)

III. Factual History

a. As Reflected in the Medical Records

S.H. was born on January 19, 2015 by cesarean section. (Ex. 2, p. 4.) She had no significant health issues at the time of her birth beyond a minor heart murmur and a ventricular septal defect ("VSD"). (*Id.* at 4-8.) S.H. was discharged home with her parents on January 23, 2015. (*Id.*) S.H. continued to receive regular wellness-checks after her discharge with no major abnormalities. (*See* Ex. 3, pp. 2-12, 13-16, 43-47.) S.H. also received a pediatric cardiology consult for her VSD from Dr. Joseph Mares. (Ex. 3, pp. 30-37.) During this visit, S.H.'s exam was normal, and Dr. Mares believed that her VSD would ultimately resolve on its own. (*Id.*) Petitioner received an EKG from Dr. Mares on February 24, 2015, which showed that her VSD was indeed getting smaller. (*Id.* at 64.)

S.H. received her first doses of the subject vaccinations, without issue, during her 2-month well child visit on March 20, 2015. (Ex. 3, pp. 88-94.) S.H. then received the

[3] This decision was subsequently vacated by the Federal Circuit for unrelated reasons. *See Kottenstette v. Sec'y of Health & Human Servs.*, 861 Fed. App'x 433 (Fed. Cir. 2021).

second doses of the subject vaccinations at her 4-month well child visit on May 22, 2015. (*Id.* at 110-16.) S.H. was brought to the emergency room several hours after receiving her May 22 vaccinations. (Ex. 4, pp. 5-59.) Petitioner reported that, after her vaccinations, S.H. experienced a "[generalized tonic-clonic] seizure with eyes rolling back, lasting 2-3 min, in afternoon while in car seat." (*Id.* at 6.) S.H. was taken to the emergency department at PIH Health Hospital ("PIH") where she had a second seizure that lasted about one minute. (*Id.*) She underwent a CT scan and laboratory testing before being transferred to Kaiser Permanente Hospital ("Kaiser"). (*Id.*) The treating physician at Kaiser, Christopher Chinnici, M.D., noted a normal exam, unremarkable laboratory testing, and no abnormalities on S.H.'s CT scan and believed that S.H.'s seizures were provoked by her vaccinations. (*Id.* at 9-10, 54.) S.H. also received a neurology consultation from Shelley Bose, M.D., while she was at Kaiser. (*Id.* at 10-12.) Dr. Bose noted that S.H. had no concerning personal or family history that would explain her seizures, and she spoke to petitioner and her husband about the risks of vaccine provoked seizures. (*Id.* at 11.) S.H. did not experience any further seizures at this visit and was discharged on May 23, 2015, with the recommendation that petitioner continue to monitor S.H. for any further signs of seizures. (*Id.* at 10.)

Petitioner returned with S.H. to the emergency department at PIH on May 26, 2015. (Ex. 6, p. 52.) Petitioner reported to staff that S.H. had experienced another two seizures that morning. (*Id.*) Petitioner described the seizures as occurring when S.H. would wake up and involving "right eye deviation, lip smacking, arms shaking," and lasting for one to two minutes. (*Id.*) S.H. did not exhibit a fever or lethargy on this visit, and her physical exam was normal. (*Id.*) Petitioner's CSF panel did reveal "some atypical cells concerning for possible leukemia," but the attending pathologist believed the results were due to a traumatic spinal tap. (*Id.* at 53.) During her observation period, S.H. did not exhibit any signs of seizure, and an attending nurse wrote that she was unable to identify any seizure activity during one period where S.H.'s parents believed that she was experiencing another seizure. (Ex. 4, p. 85.) S.H. was subsequently transferred to Kaiser for further observation. (*Id.* at 70.)

On admission at Kaiser, petitioner attributed S.H.'s seizures to her vaccinations, and explained that she believed S.H. had "been having subacute spells for a longer time and more frequently as she describes her often waking with stiff extremities and lip smacking, and possibly staring, but no obvious [generalized tonic-clonic] motions." (Ex. 4, pp.74-75.) S.H's exam was normal and no further seizures were reported. (*Id.* at 78.) S.H. also underwent a 24-hour EEG on May 27, 2015. (*Id.* at 81-82.) Although petitioner believed that S.H. experienced multiple seizures during the monitoring phase of her EEG, there were no signs of any seizure activity. (*Id.*) The treating physician at Kaiser, Dr. Fuqua, noted that "the spells being described may or may not be seizures, as mother does not report [S.H.] is sleepy or inactive (eg postictal) after." (*Id.* at 79.) S.H. was ultimately diagnosed with "absence epilepsy" and discharged home on May 27, 2015. (*Id.* at 78-79.)

The following day, S.H. was again brought to the emergency department at PIH with complaints of a generalized tonic-clonic seizure. (Ex. 6, p. 109.) Petitioner

explained that as S.H. woke up in the morning, her "eyes rolled up, her arms were tight with increased tone in her arms and legs were trembling lasting from 1-2 minutes." (*Id.*) S.H. was observed and her neurologist, Dr. Bose, was contacted.[4] (*Id.* at 110.) Dr. Bose recommended starting S.H. on phenobarbital and possibly adding Keppra at a later date. (*Id.*) S.H. was transferred to Kaiser for observation and did not exhibit any further seizures after receiving her initial phenobarbital dose. (Ex. 4, pp. 158-61.) S.H. was discharged on May 30, 2015, with an updated diagnosis of epilepsy and a prescription for phenobarbital. (*Id.* at 148-58.)

S.H. was next brought to neurologist Mi-Kyung Lee, M.D., on June 4, 2015, for a follow up on her seizures. (Ex. 5, p. 2.) Dr. Lee noted that the seizures were "initially attributed to vaccines but persisted well after 72 hours," and that S.H. had no problems with her phenobarbital prescription beyond mild drowsiness. (*Id.*) S.H. underwent a second 24-hour EEG on June 24, 2015, the results of which were normal. (*Id.* at 36-37.) On June 26, 2015, petitioner called Dr. Bose's office to report what she believed to be another seizure where S.H. "shook her hands from side to side lasting 3 to 5 seconds when she was falling asleep and bottle was being removed." (*Id.* at 23.) Dr. Bose advised petitioner to continue monitoring the event and to film it if possible, but "based on the description, [Dr. Bose was] not convinced it represents a seizure." (*Id.* at 22.) Petitioner emailed Dr. Bose again on July 16, 2015, referencing a German case study documenting an afebrile seizure in a vaccinee within 7 days after administration of the Pediarix vaccine and asking if S.H.'s seizures could have been caused by her vaccinations. (*Id.* at 42-43.) She further requested a referral for S.H. to see Dean Sarco, M.D., for a second opinion. (*Id.*) Dr. Bose responded that a single case report is insufficient to attribute causation to the vaccines; however, she referred S.H. to Dr. Sarco as requested. (*Id.*)

On July 24, 2015, S.H. was seen by Jennifer Varghese, M.D., for head control problems. (Ex. 5, p. 61.) Dr. Varghese reviewed videos that petitioner had taken of S.H. and concluded that, despite there appearing to be some lack of head control, there was no seizure activity and S.H. appeared to be developing normally. (*Id.* at 62.) Dr. Varghese's assessment was "PERSON W FEARED COMPLAINT," and she declined to make a diagnosis. (*Id.*)

S.H. saw Dr. Sarco on July 27, 2015, for a second opinion on her epilepsy. (Ex. 5, p. 69.) Dr. Sarco recorded a normal exam and noted that it was unclear if S.H.'s seizures were caused by her vaccinations or were secondary to a mild epilepsy. (*Id.* at 71.) He suspected that S.H. "has a mildly increased risk for seizures inherently," and recommended continuing phenobarbital at least through her 12-month vaccinations. (*Id.* at 71-72.) S.H. continued to take phenobarbital with no issues and Dr. Sarco began discussing weaning her off the medication in October of 2015, however, ultimately decided that S.H. should not be weaned until after her first year vaccinations. (*Id.* at 165, 172-74, 229.) Petitioner began weaning S.H. in the beginning of April 2016. (*Id.* at 306-08.) S.H. continued to receive her typical vaccinations on a more spread-out schedule, and there have not been any additional seizures reported since May 28,

[4] The record erroneously refers to Dr. Bose as "Dr. Boat." (Ex. 6, pp. 109-10.)

2015. (*Id.* at 154-316.) In 2017, S.H. saw a speech therapist, however, had no speech or developmental delays as a result of her seizures. (Ex. 27, pp. 399-406.)

b. As Reflected by Petitioner's Testimony

Petitioner filed an affidavit and also testified during the hearing. (Ex. 1; Tr. 6-27.)

Petitioner recounted that S.H. received her 2-month vaccinations on March 20, 2015, after which, she "was very fussy . . . and had a slight temperature." (Ex. 1, p. 2.) She further states that on May 22, 2015, she took S.H. in for her 4-month check-up where she received her 4-month vaccinations of Pediarix, HiB, Prevnar 13, and Rotarix. (*Id*.; *see also* Tr. 8.) Petitioner stated that S.H. fell asleep on the way home following her vaccinations, and that she was brought into the house in her car seat so as not to wake her. (Ex. 1, p. 2-3; *see also* Tr. 8.) About 20 minutes after arriving home, S.H. awoke and was "smacking her lips." (Ex. 1, p. 3; *see also* Tr. 9.) After several seconds of lip smacking, S.H.'s father called petitioner over to tell her something was wrong S.H. (Ex. 1, p. 3.) Petitioner stated that it was at this point she "realized that [S.H.] was having a seizure [and] immediately called 911." (*Id.*; *see also* Tr. 9.) Petitioner described S.H.'s seizure as involving her eyes rolling upward, arms and legs jerking, and smacking her lips. (Ex. 1, p. 3.) S.H. was somewhat responsive after the seizure, but she was not the happy and babbling baby that she usually was. (Tr. 9, 11.) Petitioner described how S.H. cried "really loud" after she stopped seizing, and then how she was "quieter than usual" but not quite drowsy. (*Id.* at 9-10.)

Petitioner stated that while S.H. was being prepared for discharge from PIH, she had a second seizure with the same characteristics as the first. (Ex. 1, p. 3; *see also* Tr. 11-14.) The doctors ordered a CT scan to rule out any brain bleeding, and it came back normal. (Ex. 1, p. 3; *see also* Tr. 11.) Petitioner affirmed that S.H. had a slight temperature following her second seizure and was treated with Tylenol. (Ex. 1, p. 3.) S.H. was then transferred to Kaiser where she was observed over 24 hours for any additional seizure activity. (*Id.* at 4.) Petitioner affirmed that after meeting Dr. Bose, S.H.'s pediatric neurologist, she was told that the DTaP components of the Pediarix vaccine may have triggered S.H.'s seizures. (*Id.*; *see also* Tr. 14.) S.H. did not show any signs of seizure during her observation period at Kaiser. (Ex. 1, p. 4.)

Petitioner reported that S.H. had a third seizure on May 26, 2015, with the same characteristics as her first two seizures. (Ex. 1, p. 4; *see also* Tr. 15-18.) S.H. was again taken to the PIH emergency room where she underwent a lumbar puncture and additional labs, all of which were normal. (Ex. 1, p. 4.) S.H. was subsequently transferred back to Kaiser where she underwent additional "rigorous testing" including a second lumbar puncture, overnight EEG, and MRI, all of which were normal. (*Id.* at 4-5.) S.H. was discharged on May 27, 2015. (*Id.* at 5.)

Petitioner stated that S.H. suffered a fourth seizure, with the same symptoms as her first three seizures, on May 28, 2015. (Ex. 1, p. 5; *see also* Tr. 19-23.) S.H. was first brought to PIH before being transferred to Kaiser where she was diagnosed with

epilepsy and placed on anti-convulsant medication. (Ex. 1, p. 5.) Petitioner explained that, at four months, S.H. was able to sit with assistance and had good head control. (Tr. 21.) However, after starting on phenobarbital, S.H. became extremely groggy and could no longer lift her head. (Ex. 1, p. 5; *see also* Tr. 21.) Petitioner described S.H. as being "lethargic" and "like a zombie." (Ex. 1, p. 5.) The effect of the loading dose lasted for about 24 hours before S.H. started to regain some head control, although petitioner indicated that S.H. still "was not her usual self." (Tr. 21-22; *see also* Ex. 1, p. 5.) After another day, petitioner stated that S.H. remained unusually quiet and unengaging. (Tr. 22.) S.H. continued to take phenobarbital until July 11, 2016. (Ex. 1, p. 5.) While petitioner indicated that S.H.'s demeanor "improved over months," she stated that she did not notice a big difference until after S.H. was fully weaned off the medication. (Tr. 22.) On that point, petitioner testified to the effect that phenobarbital had on S.H.'s development. (*Id.* at 23.) She stated that S.H.'s speech was not developing as it should and that S.H. was stuttering "a lot." (*Id.*) After discontinuing the medication, S.H. has been hitting her milestones despite continuing to stutter. (*Id.*)

Petitioner stated that S.H. has not suffered any additional seizures since May 28, 2015. (Ex. 1, p. 6.) Petitioner further stated that she sought a second opinion from Dr. Sarco, who stated that there was a possibility that S.H.'s May 22 vaccinations caused her seizures. (*Id.*) After seeing Dr. Sarco, petitioner sought genetic testing for S.H. from Dr. Loree Willis, the results of which were normal. (*Id.*)

IV. Expert Opinions

a. Petitioner's Expert, Marcel Kinsbourne, M.D.[5]

Petitioner filed a series of expert reports from pediatric neurologist Dr. Marcel Kinsbourne to support her claim. (*See* Exs. 7, 24, 28, 45.) Dr. Kinsbourne also provided testimony at the entitlement hearing, during which he was offered without objection as an expert in pediatric neurology. (Tr. 31-76.)

[5] Dr. Kinsbourne received his Bachelor's degree from Christ Church College at Oxford University in 1952 and his first medical degree from Oxford University Medical School in 1955. (Ex. 2, p. 1.) He also holds two other advanced degrees from Oxford, and a second medical degree from the "State of North Carolina" which was conferred in 1967. (*Id.*) He is licensed in the United Kingdom, State of North Carolina, Commonwealths of Massachusetts and Virginia, and by the Medical Council of Canada. (*Id.*) He is board certified by the Royal College of Physicians in London, the Educational Council for Foreign Medical Graduates, and the American Board of Pediatrics. (*Id.*) Dr. Kinsbourne has held numerous academic positions throughout his career including professorships and lecturer positions in psychology, neurology, and pediatrics at Oxford University, the University of Toronto, Harvard Medical School, Brandeis University, Boston University, Clark University, Tufts University, and the University of Waterloo. (*Id.* at 1-3.) He has also held appointments at a similarly broad slate of hospitals including fellowships and directorships in several areas of neurology at Boston University, the Eunice Kennedy Shriver Center, and Duke University. (*Id.*) Dr. Kinsbourne has published extensively on pediatrics, neurology, and psychology as the primary or supporting author on 425 pieces of peer reviewed medical literature. (*Id.* at 6-39.)

i. Dr. Kinsbourne's initial report

Although S.H. received multiple vaccinations at her four-month well visit, Dr. Kinsbourne's initial report discusses only the DTaP vaccine as potentially causal. (Ex. 7.) Dr. Kinsbourne opines that S.H.'s first seizure, which was an afebrile seizure occurring less than one hour after her DTaP vaccination, was vaccine-caused. (*Id.* at 2.) He cites two papers to support his general proposition that brief afebrile seizures can be temporally associated with vaccinations such as the DTaP vaccine. (*Id*. (citing Sarah von Spiczak et al., *A Retrospective Population-Based Study on Seizures Related to Childhood Vaccination,* 52 EPILEPSIA 1506 (2011) (Ex. 20); D T. Hsieh et al., *New-Onset Afebrile Seizures in Infants*, 74 NEUROLOGY 150 (2010) (Ex. 13).)[6] Dr. Kinsbourne indicates that post-vaccination seizures typically occur within 72 hours of vaccination, and most often occur within 24 hours of vaccination. (Ex. 7, p. 4.) He acknowledged that the available epidemiology does not break down data by hour, but cited one study that observed seizures following the whole cell pertussis vaccine and noted the shortest interval was one hour. (*Id*. (citing Jerome V. Murphy, Larrie D. Sarff, & Kathleen M. Marquardt, *Recurrent Seizures After Diphtheria, Tetanus, and Pertussis Vaccine Immunization*, 138 AM. J. DISEASES CHILDREN 908 (1984) (Ex. 18).) He urges that there is no minimal interval for seizures to occur following pertussis vaccinations. (*Id*.)

Further, Dr. Kinsbourne asserts that there is an increased risk of seizures following receipt of vaccines containing acellular pertussis. (Ex. 7, p. 3.) Relying on a higher risk of seizures following the older whole cell formulation of the pertussis vaccine, Dr. Kinsbourne cites several additional studies for the proposition that the acellular formulation reduced, but did not eliminate, the risk. (*Id*. (citing Nicole Le Saux et al., *Decrease in Hospital Admissions for Febrile Seizures and Reports of Hypotonic-Hyporesponsive Episodes Presenting to Hospital Emergency Departments Since Switching to Acellular Pertussis Vaccine in Canada: A Report from IMPACT*, 112 PEDIATRICS e348 (2003) (Ex. 17); Lisa A. Jackson et al., *Retrospective Population-Based Assessment of Medically Attended Injection Site Reactions, Seizures, Allergic Responses and Febrile Episodes After Acellular Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids*, 21 PEDIATRIC INFECTIOUS DISEASE J. 781 (2008) (Ex. 15); M. Miles Braun et al., *Infant Immunization with Acellular Pertussis Vaccines in the United States: Assessment of the First Two Years' Data From the Vaccine Adverse Event Reporting System (VAERS)*, 106 PEDIATRICS 1 (2000) (Ex. 9); Dennis A. Conrad & Hal B. Jensen, *Using Acellular Pertussis Vaccines for Childhood Immunizations: Potential Benefits Far Outweigh Potential Risks*, 105 POSTGRADUATE MED. 1 (1999) (Ex.

[6] It should be noted that, while the von Spiczak et al. study identifies some children with afebrile seizures following vaccination, it does not engage in any statistical analysis of the data. (von Spiczak et al., *supra,* at Ex. 20.) The purpose of the paper was only to describe the clinical features of children having reported seizures or epilepsies that occurred after vaccination. (*Id.* at 1.) Similarly, the Hsieh et al. paper examines the presenting characteristics of new-onset afebrile seizures in infants. (Hsieh et al., *supra,* at Ex. 13.) It does not discuss vaccines at all, let alone ascribe afebrile seizure activity to vaccines. (*Id.*)

11)).)[7] Dr. Kinsbourne opines that the pertussis toxin is toxoided in the acellular pertussis vaccine; however, some toxoid spontaneously reverts to toxin. (*Id.* (citing Michael J. Corbel & Dorothy K. L. Xing, *Toxicity and Potency Evaluation of Pertussis Vaccines*, 3 EXPERT REV. VACCINES 89 (2004) (Ex. 12); Chun-Ting Yeun et al., *An* In Vitro *Assay System as a Potential Replacement for the Histamine Sensitisation Test for Acellular Pertussis Based Combination Vaccines*, VACCINE (2010) (Ex. 23)).) Dr. Kinsbourne would later disclaim this toxin reversion theory during the hearing. (Tr. 65.)

According to Dr. Kinsbourne, the pertussis toxin "has a selective negative effect on inhibitory (GABergic) synapses" and can "attach to the G-protein element of neuronal membrane receptors, setting up a chemical cascade such that the action of inhibitory neurotransmitters is impaired," while "the action of excitatory neurotransmitters is enhanced." (Ex. 7, p. 3.) This ultimately causes a neurotransmitter imbalance in the brain that favors excitation, and thus increases the risk of seizure activity. (*Id.* (citing Austin Legido et al., *Autoimmune and Postinfectious Diseases*, CHILD NEUROLOGY (2006) (Ex. 16)).) Further, he explains that pertussis toxin has an adjuvant effect on the production of cytokines, including the pro-inflammatory interleukin-1 beta ("IL-1β"), which has known epileptogenic properties. (*Id.*)

Dr. Kinsbourne further explains that vaccinations trigger an innate immune system response, which includes the release of proinflammatory cytokines including IL-1β. (Ex. 7, p. 3 (citing Xin Chen O.M. Zack Howard, & Joost J. Oppenheim, *Pertussis Toxin by Inducing IL-6 Promotes the Generation of IL-17-Producing CD4 Cells*, 178 J. IMMUNOLOGY 6123 (2007) (Ex. 10)).) He suggests that, while IL-1β mediates fever, it also mediates seizures because IL-1β has the propensity to cause seizures and seizures have the propensity to release additional IL-1β. (*Id.* (citing Annamaria Vezzani & Tallie Z. Baram, *New Roles for Interleukin-1 Beta in the Mechanisms of Epilepsy*, 7 EPILEPSY CURRENTS 45 (2007) (Ex. 22)).) IL-1β receptors are expressed in the hippocampus, which is a particularly seizure sensitive region of the brain. (Vezzani & Baram, *supra,* at Ex. 22.) When IL-1β binds to its receptor, it reduces GABA currents, which results in diminished inhibition and increased excitability, ultimately decreasing the subject's seizure threshold. (*Id.* (citing Natalie T. Sanon, Sebastien Desgent, & Lionel Carmant, *Atypical Febrile Seizures, Mesial Temporal Lobe Epilepsy, and Dual*

[7] It has been observed in prior cases, however, that these studies do not support Dr. Kinsbourne's assertion because they do not confirm whether the much lower incidences of seizures following acellular pertussis remain above background rates. *See, e.g. Bangerter ex rel. D.B. v. Sec'y of Health & Human Servs.*, No. 15-1186V, 2022 WL 439535, at *21-23 (Fed. Cl. Spec. Mstr. Jan. 18, 2022); *Vinesar v. Sec'y of Health & Human Servs.,* No. 18-440V, 2023 WL 5427935, at *28-31 (Fed. Cl. Spec. Mstr. July 28, 2023), *motion for review filed* (Oct. 1, 2023). As Dr. Kinsbourne highlighted by his citation to Hsieh et al., childhood seizures occur most commonly in infancy (up to 24 months of age) irrespective of vaccination. (Hseih et al., *supra,* atEx. 13, pp. 2-3.) In his second report, Dr. Kinsbourne added a further citation to a study by Uberall et al. (Ex. 24, p. 2 (citing *See* M.A. Uberall et al., *Severe Adverse Events in a Comparative Efficacy Trial in Germany in Infants Receiving Either the Lederle/Takeda Acellular Pertussis Component DTP (DTaP) Vaccine, the Lederle Whole-Cell Component DTP (DTP) or DT Vaccine. The Pertussis Vaccine Study Group.*, 89 DEV. BIOLOGY STANDARDIZATION 83 (1997) (Ex. 25)).) However, only the abstract was filed. The abstract is limited to indicating that convulsions within three days of the DTaP vaccine were five times lower than with the whole cell DTP vaccine. (Uberall et al., *supra,* at Ex. 25.)

Pathology, 2012 EPILEPSY RES. & TREATMENT 1 (2012) (Ex. 19)).) Dr. Kinsbourne explains that, among those whose "GABergic neurons [are] already compromised, as in some SCN1A mutations in children," this can result in seizures.[8] (*Id.*)

ii. Dr. Kinsbourne's first supplemental report

In his second report, Dr. Kinsbourne primarily addresses Dr. Holmes' assertion that S.H. suffered paroxysmal events rather than seizures. He confirms the five specific events he concludes were seizures: May 22, 2015 at about 10:30am[9] (Ex. 24, p. 1 (citing Ex. 6, pp. 3-6, 8-9)); May 22, 2015, at 3:50PM (*Id*. (citing Ex. 6, pp. 3-6, 8-9, 19-20)); May 26, 2015 (two seizures) (*Id*. (citing Ex. 6, pp. 52-53)); and May 28, 2015 (*Id*. (citing Ex. 6, pp. 109-11)). Dr. Kinsbourne stresses that the treating physicians considered S.H.'s events to be seizures and indicates that his review of the literature failed to confirm a postictal period as a diagnostic requirement for a generalized seizure. (*Id*.) To the extent Dr. Holmes cited a comment by Dr. Fuqua doubting that S.H. was experiencing seizures, Dr. Kinsbourne indicates the comment was in relation to separate "subacute spells" and not the events he has identified as seizures.[10] (*Id*. at 2 (discussing Ex. 4, pp. 77-79).)

Dr. Kinsbourne further opines that S.H.'s seizures meet the criteria for epilepsy. (Ex. 24, p. 2.) Additionally, he opines that, because the first two onset seizures were caused by the DTaP vaccine, "and the subsequent seizures were similar in nature to the onset seizures, it follows that the vaccinations triggered [S.H.]'s epilepsy." (*Id*.) Dr. Kinsbourne reiterated his reliance on a heightened incidence of post-DTaP seizures among children with SCN1A genetic variants. (*Id*.)

iii. Dr. Kinsbourne's second supplemental report

Dr. Kinsbourne's third report (Ex. 28) answered several follow up questions posed by my October 9, 2020 order. (*See* ECF No. 41.) Dr. Kinsbourne was asked to explain why his opinion offered in this case was not incompatible with the opinion he

[8] The SCN1A gene variant causes a syndrome that is known as "Dravet syndrome." This gene variant and the resulting Dravet syndrome have been the subject of many prior decisions within this program. *See, e.g.*, *Vinesar,* 2023 WL 5427935; *Thompson v. Sec'y of Health & Human Servs.*, No. 15-671V, 2023 WL 21234 (Fed. Cl. Spec. Mstr. Jan 3, 2023); *Oliver v. Sec'y of Health & Human Servs.*, No. 10-394V, 2017 WL 747846 (Fed. Cl. Spec. Mstr. Feb. 1, 2017), *aff'd*, 133 Fed. Cl. 341 (2017), *aff'd*, 900 F.3d 1357 (Fed. Cir. 2018); *Faoro v. Sec'y of Health & Human Servs.*, No. 10-704V, 2016 WL 675491 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *motion for review denied*, 128 Fed. Cl. 61 (2016); *Barclay v. Sec'y of Health & Human Servs.*, No. 07-605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014), *motion for review denied*, 122 Fed. Cl. 189 (2015). There is no evidence in this case that S.H. carries this type of gene variant or suffers this syndrome.

[9] Regarding Dr. Holmes's emphasis on the significance of postictal periods, Dr. Kinsbourne interprets a notation that "she was a little bit sleepy" following the event as a postictal period. (Ex. 24, p.1.)

[10] I do note that Dr. Kinsbourne further addressed some of these points in his fourth report. (*See* Ex. 45, p. 2.) However, it is not necessary to separately summarize this aspect of the later report.

offered in a prior case, *Fuller ex rel. B.F. v. Secretary of Health and Human Services*. (*Id.* (citing No. 15-1470V, 2019 WL 7576382, at *8-9 (Fed. Cl. Spec. Mstr. Dec. 17, 2019).) In that case, Dr. Kinsbourne appeared to opine that fever itself is implicated in the process by which vaccines can cause seizures and further that it is complex[11] febrile seizures that can result in epilepsy. (*Id.* (discussing *Fuller ex rel B.F.*, 2019 WL 7576382).)

Dr. Kinsbourne cited three studies to demonstrate that the effects of IL-1β in causing fever and seizure are distinct despite often occurring concurrently. (Ex. 28, pp. 1-2 (citing C. Dube, et al., Commentary, *Cytokines: A Link Between Fever and Seizures*, 5 EPILEPSY CURRENTS 169 (2005) (Ex. 33); Celine Dube et al*., Interleukin-1β Contributes to the Generation of Experimental Febrile Seizures*, 57 ANNALS NEUROLOGY 152 (2005) (Ex. 48); Vezzani & Baram, *supra,* at Ex. 22).) Dr. Kinsbourne agreed that complex seizures are more likely to lead to epilepsy. (*Id*. at 2.) He indicated that the risk of future unprovoked seizures following a simple febrile seizure is 2.5% compared to a 1.4% risk among the general population whereas the risk of future unprovoked seizures following complex febrile seizures is between 6-49% depending on additional factors. (*Id*. at 3.) Dr. Kinsbourne opined that S.H.'s initial onset seizure had focal features and recurred within 24 hours and was therefore complex, although it was not accompanied by an elevation in temperature. (*Id.*) During the hearing, Dr. Kinsborne would instead later acknowledge that S.H.'s seizures were generalized clonic-tonic seizures. (Tr. 33, 60.)

Dr. Kinsbourne was also prompted to substantiate two additional points raised by his prior reports. (ECF No. 41, pp. 1-2.) First, he was directed to substantiate, vis-à-vis his comparison between the relative risk of seizures following whole cell versus acellular pertussis vaccine, that the lower incidences of post-DTaP seizures remained above either control or background rates. (*Id.*) He confirmed that he cannot and that he therefore is "not in a position to rely on epidemiologic evidence on this issue." (Ex. 28, p. 4.) Additionally, Dr. Kinsbourne cited heightened seizure activity among SCN1A gene variant carriers without supporting literature or explaining how the assertion is relevant to S.H. given his acknowledgement that she does not carry that gene variant. (ECF No. 41, p. 2.) Dr. Kinsbourne discussed studies that he indicated show that, while Dravet syndrome patients are at "striking liability to febrile seizures," a significant portion of post-DTaP seizure onset in Dravet syndrome occurred via afebrile seizures. (Ex. 28, p. 4.) Combined with an additional study by Berg et al., Dr. Kinsbourne asserts that this is relevant to S.H.'s case because it shows that "children whose seizures occur with relatively low fever grades require less provocation to have a seizure than do those whose initial seizures occurred at higher temperatures." (*Id.* at 5 (citing Anne T. Berg et al., *Predictors of Recurrent Febrile Seizures: A Prospective Cohort Study*, 151 ARCHIVES PEDIATRIC & ADOLESCENT MED. 371 (1997) (Ex. 29).) Therefore, because the medical literature supports the notion that Dravet syndrome patients experience afebrile

[11] Dr. Kinsbourne explains that for generalized seizures, simple febrile seizures are considered uncomplicated convulsions that persist for less than 10-15 minutes. (Ex. 28, pp. 2-3.) Complex seizures are those that last longer. For partial afebrile seizures are complex if there is a loss of consciousness and simple if not. (*Id.*) The terms simple and complex are applied only to febrile seizures. (Ex. D, p. 3.)

seizures due to having a lowered seizure threshold, "S.H.'s afebrile seizure onset during infancy simply indicates that she had a lower than usual seizure threshold at that early stage in her development." (*Id*. at 6.)

iv. Dr. Kinsbourne's third supplemental report

In his fourth report, Dr. Kinsbourne revised his opinion to indicate that he believes that S.H.'s condition could also have been caused by her Prevnar 13 vaccine either alone or in combination with her DTaP vaccination. (Ex. 45, p. 3.) Dr. Kinsbourne cites additional studies for the proposition that the Prevnar 13 vaccine has been associated with increased risk of *febrile* seizures.[12] (*Id*. (citing Robert P. Wise et al., *Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine*, 292 JAMA 1702 (2004) (Ex. 53); Jonathan Duffy et al., *Febrile Seizure Risk After Vaccination in Children 6 to 23 Months*, 138 PEDIATRICS (2016) (author manuscript) (Ex. 50); Meghan A. Baker, et al., *The Risk of Febrile Seizures Following Influenza and 13-Valent Pneumococcal Conjugate Vaccines*, 38 VACCINE 2166 (2020) (Ex. 46)).) He also reiterated his assertion that the reduction in seizures following the change from DTP to DTaP vaccination evidences that the DTaP vaccine causes seizures. (*Id.*) He asserts that "[m]any studies have shown that vaccinations cause seizures and many of those studies had appropriate controls." (*Id.*) As an example, he cites Sun et al., which showed an increased incidence of *febrile* seizures following DTaP vaccination. (*Id.* (citing Yuelian Sun et al., *Risk of Febrile Seizures and Epilepsy After Vaccination with Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and* Haemophilus Influenzae *Type B*, 307 JAMA 823 (2012) (Ex. 21).) Dr. Kinsbourne further cites Wang, et al., for the proposition that there is an increased risk of seizures one day following both DTaP and Prevnar 13 vaccines. (*Id*. at 4 (citing Shirley V. Wang et al., *Determining Which of Several Simultaneously Administered Vaccines Increase Risk of an Adverse Event*, 43 DRUG SAFETY 1057 (2020) (Ex. 52).) Importantly, the Wang study does not specifically implicate afebrile seizures but merely fails to distinguish between febrile and afebrile seizures. (Wang et al., *supra,* at Ex. 52.)

Dr. Kinsbourne reiterates his reliance on research from Vezzani group to support that idea that "the flow of cytokines to the hypothalamic control center for temperature and the flow of cytokines to hippocampal and neocortical seizure generators are independent of each other." (Ex. 45, p. 4 (citing Vezzani & Baram, *supra,* at Ex. 22).) He further opines that "the lower the seizure threshold is, the less inflammation it takes to provoke a seizure." (*Id*.) He stresses the findings of the study by Dube et al., which he asserts support the idea that fever "usually accompanies the seizure but does not cause it." (*Id*. at 5 (citing Dube, et al., *supra,* at Ex. 33).) He summarized his opinion as follows:

[12] Dr. Kinsbourne also notes that 19 cases of afebrile seizure following Prevnar were noted in the Wise study. (Ex. 45, p. 3 (citing Wise et al., *supra,* at Ex. 53, p. 6).) Importantly, however, the authors do not ascribe causation. Remarking on the total number of reported seizures – the majority of which were febrile – they note that "[l]ike other vaccines, PCV can provoke fever, which could trigger a febrile seizure." (Wise et al., *supra* Ex. 53, p. 8.)

> [S.H.] probably had a lower-than-normal seizure threshold before she received her May 22, 2015 vaccination and the vaccinations further lowered the threshold to the tipping point. This conclusion is based on: 1. the fact that she had seizures at all; 2. that she had a seizure so quickly after the vaccinations; and 3. that she had a seizure without a clear fever. It suggests that [S.H.] was on the edge and only needed a small nudge to go over the edge (and have a seizure).

(*Id*.at 5-6.) Dr. Kinsbourne further opined that each seizure produces more inflammatory cytokines and, therefore, S.H.'s subsequent seizures were due at least in part to the inflammation resulting from her first seizures. (*Id*. at 6.) Accordingly, "[s]ince the vaccination caused the first seizure it was a substantial factor in the cause of them all." (*Id*.)

v. Testimony

At the entitlement hearing, Dr. Kinsbourne testified that S.H. experienced generalized tonic-clonic seizures "[w]ithout any doubt." (Tr. 33.) He further testified that "there is a somewhat disproportionate risk of seizure activity within a day" of receiving the acellular pertussis vaccine, pneumococcal vaccine, "or both." (*Id.* at 36.) However, he noted that afebrile seizure following vaccination is "fairly unusual" in young children and does not "rise to a level that will be picked up in epidemiological studies."[13] (*Id.* at 36.) Dr. Kinsbourne acknowledged that the seizure threshold in young children is generally "fairly low," and it can be so low in some cases that onset of seizure activity can precede fever or occur in the absence of fever. (*Id.* at 38.) He explained that this is because the fever does not usually generate the seizure. (*Id.*) Instead, proinflammatory cytokines, which are released by vaccinations, cause both the fever and the seizure "by influencing the function of two different parts of the brain." (*Id.*)

He further testified that, in the case of vaccine-caused seizure activity, onset often occurs within "a matter of hours," and that there is "no way of rationalizing" the concept that onset could be too soon to be vaccine caused. (Tr. 48.) Although he recognized that it takes time for the body to create proinflammatory cytokines in response to vaccination, Dr. Kinsbourne explained that how much time it takes for fever to set in is irrelevant to this case as any fever would be a "byproduct" of the process by which a vaccine can cause a seizure. (*Id.* at 49.)

Dr. Kinsbourne testified that S.H. likely had a low seizure threshold based on the abruptness of onset and the lack of any documented fever. (Tr. 45.) He analogized S.H.'s course to that of an infant with an SCN1A gene variation because children with this gene are prone to afebrile seizures triggered by their 4-month vaccinations. (*Id.* at 43.) Though he acknowledged that S.H. does not have any genetic abnormalities that would cause her to be particularly susceptible to seizures, Dr. Kinsbourne suggested

[13] During the hearing, Dr. Kinsbourne specifically disavowed his claim in his earlier reports that the pertussis toxoid in the DTaP vaccine can spontaneously revert to pertussis toxin. (Tr. 64-65.) This assertion had informed his interpretation of the epidemiologic data.

that onset was so rapid that "one can't imagine any other interfering process that could have caused" the seizures. (*Id.* at 43.) However, in response to the undersigned's questions, Dr. Kinsbourne indicated that S.H.'s course could not ultimately be distinguished from benign epilepsy of childhood, apart from onset of multiple seizures having occurred on the day of vaccination. (*Id.* at 75.)

Dr. Kinsbourne explained that the seizures themselves lower the seizure threshold and make subsequent events more likely. (Tr. 52.) In essence, he testified that "seizure begets seizure," such that the occurrence of one seizure changes the brain in a way that favors another seizure occurring and so on. (*Id.* at 69-70.) He further explained that epilepsy is a self-sustaining process whereby one does not require a trigger for seizure activity to occur. (*Id.* at 72.) Dr. Kinsbourne testified that it is customary to keep a child on anti-seizure medication until they have been free from seizures for at least a year. (*Id.* at 52-53.) He acknowledged that there is no record that supports the contention that S.H. suffered any adverse effects as a result of taking phenobarbital. (*Id.* at 57.) However, Dr. Kinsbourne testified that discontinuing phenobarbital without any subsequent seizures is what represents confirmation of epilepsy remission. (*Id.* at 70.)

b. Respondent's Expert, Gregory Holmes, M.D. [14]

In support of his position, respondent filed several expert reports by pediatric neurologist Dr. Gregory Holmes. (Exs. A, C, D.) Dr. Holmes also provided testimony at the entitlement hearing, during which he was offered without objection as an expert in pediatric neurology, with an additional specialty in seizure disorders. (Tr. 77-129.)

i. Dr. Holmes' initial report

Dr. Holmes opines that what petitioner describes as seizures were actually "paroxysmal events of unknown etiology." (Ex. A, p. 10.) He does not believe that "[t]he semiology of the events" is suggestive of epilepsy and emphasizes the fact that there has been no corroborative testing indicating an epileptic condition. (*Id.*) Dr. Holmes notes that the first event ended with S.H. crying, whereas generalized seizure disorder

[14] Dr. Holmes received his bachelor's degree from Washington & Lee University in 1970, and his medical degree from the University of Virginia in 1974. (Ex. B, p. 1.) Dr. Holmes also received an honorary medical degree from Harvard University in 1996. (*Id.*) Dr. Holmes served as an intern and resident in pediatrics at Yale University School of Medicine from 1974 to 1976 before moving on to the University of Virginia School of Medicine to serve as a resident in pediatric neurology from 1976 to 1979. (*Id.*) He is licensed in Connecticut, Georgia, Massachusetts, New Hampshire, and Vermont, and board certified by the American Boards of Pediatrics, Psychiatry and Neurology, and Clinical Neurophysiology. (*Id.*) Dr. Holmes has held professorships in Neurology and Pediatrics at the University of Connecticut, the Medical College of Georgia, Harvard Medical School, Dartmouth Medical School, and the University of Vermont College of Medicine. (*Id.* at 2.) He has served as a staff neurologist and director of various neurology and neurophysiology labs at eight different hospitals in five different states, including at the Children's Hospital of Boston, Massachusetts and the Dartmouth-Hitchcock Medical Center in New Hampshire. (*Id.*) Dr. Holmes has contributed to 312 pieces of peer-reviewed medical literature on pediatrics and neurology as either the sole, primary, or supporting author. (*Id.* at 40-65.)

"inevitably is associated with postictal unresponsiveness or stupor." (*Id.* at 10-11.) The second event, which was observed by hospital staff, also lacked a postictal state. (*Id.*) According to Dr. Holmes, the lack of a postictal state following alleged convulsions "argues strongly against an epileptic event." (*Id.* at 11 (citing Makram Obeid & Mohamad A. Mikati, *Expanding Spectrum of Paroxysmal Events in Children: Potential Mimickers of Epilepsy*, 37 PEDIATRIC NEUROLOGY 309 (2007) (Ex. A, Tab 1)).) Dr. Holmes also highlights S.H.'s EEG results, explaining that it is very unlikely for an infant with epilepsy to be monitored for two 24-hour periods without any signs of epilepsy or seizure.[15] (*Id.*; *see also* Tr. 91.) Further, paroxysmal events in children may mimic epileptic seizures and are only now being more widely recognized; nonepileptic paroxysms may present with drop attacks, limb or eye jerks, and abnormal postures. (Ex. A, p. 11 (citing Obeid & Mikati, *supra,* at Ex. A, Tab 1).) Dr. Holmes submits that there is no indication in the medical record that S.H.'s vaccinations were in any way related to her paroxysms which were, by Dr. Holmes' description, a "benign, self-resolving condition." (*Id.*)

Dr. Holmes explains that a link between DTaP and seizures has not yet been discovered with any certainty and cites an Institute of Medicine ("IOM") Review of Adverse Effects of Vaccines, which noted that the available studies alleging any such link were not rigorous enough to be reliable. (Ex. A, p. (citing COMM. TO REV. ADVERSE EFFECTS OF VACCINES, INST. OF MED., ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY (Kathleen Stratton et al. eds., 2012) (Ex. A, Tab 9) [hereinafter IOM review].) Further, the IOM found no evidence connecting the mechanisms of seizures or epilepsy to any of the vaccines that S.H. received. (*Id.*) The only study that the IOM perceived as methodologically sound failed to identify an increased risk of seizures in DTaP vaccinated infants 6 weeks to 23 months. (*Id.* at 11-12 (citing Wan-Ting Huang et al., *Lack of Association Between Acellular Pertussis Vaccine and Seizures in Early Childhood*, 126 PEDIATRICS e263 (2010) (Ex. A, Tab 12)).)

Dr. Holmes explains that the primary study cited in Dr. Kinsbourne's first report to support a temporal relationship between vaccinations and seizures was not particularly rigorous and amounted to a retrospective review of a case report database of adverse events without any sort of non-immunized control group. (Ex. A, p. 12 (citing von Spiczak, *supra,* at Ex. 20).) Dr. Holmes reiterates the IOM findings that virtually all of the available epidemiological studies either had similar issues in that they came from passive surveillance programs and lacked control groups, had "serious methodological limitations," or combined coma and seizure symptoms in the analysis and failed to properly explain how cases were selected. (*Id.* (citing IOM review, *supra,* at Ex. A, Tab

[15] Dr. Holmes acknowledges that children can have epilepsy with normal EEGs, but that such results make the likelihood of epilepsy "quite low." (Ex. A, p. 12 (citing Pradeep N. Modur & Barbara Rigdon, *Diagnostic Yield of Sequential Routine EEG and Extended Outpatient Video-EEG Monitoring*, 119 CLINICAL NEUROPHYSIOLOGY 190 (2008) (Ex. A, Tab 15); Elaine Wirrell et al., *Ambulatory Electroencephalography (EEG) in Children: Diagnostic Yield and Tolerability*, 23 J. CHILD NEUROLOGY 655 (2008) (Ex. A, Tab 16); S.J.M. Smith, *EEG in the Diagnosis, Classification, and Management of Patients with Epilepsy*, 76 J. NEUROLOGY NEUROSURGERY & PSYCHIATRY ii2 (2005) (Ex. A, Tab 17); Audrey Riquet et al., *Usefulness of Video-EEG Monitoring in Children*, 20 SEIZURE 18 (2011) (Ex. A, Tab 18)); *see also* Tr. 91.)

9).) Dr. Holmes explains that the Sun study cited by Dr. Kinsbourne fails to support petitioner's claim because it focuses on an increased risk in febrile seizures while S.H. did not experience seizures, and if she did, they were certainly not febrile. (*Id.* at 13 (citing Sun et al., *supra,* at Ex. 21).)

Finally, Dr. Holmes questions Dr. Kinsbourne's proposed theory. Dr. Holmes explains that, in referencing the evidence he cited to explain how pertussis toxin can facilitate increased seizure activity, Dr. Kinsbourne fails to include a passage that reads:

> Whereas in the vast majority of cases the blood-brain barrier prevents entry of the toxin into the brain, its temporary disruption with a concomitant viral disease or fever or a response to the endotoxin present in the vaccine could well facilitate access of pertussis toxin to the nerve cells. Such a disruption has been seen in pertussis encephalopathy, in which high CSF antibody titers to pertussis toxin have been demonstrate[d].

(Ex. A, p. 12 (quoting Legido et al., *supra,* at Ex. 16, p. 3).) Dr. Holmes notes that S.H. did not have a viral illness, fever, or pertussis encephalopathy. (*Id.*) Further, Dr. Holmes writes that there is no evidence that the endotoxin found in attenuated pertussis vaccines alters G-protein coupled receptors or inactivates G-proteins. (*Id.* at 12-13.) Dr. Holmes also points out that Dr. Kinsbourne relied on a passage from the Legido chapter, which states that initial seizures occur within 24 hours of immunization; however, this passage, when taken in context, refers to whole-cell pertussis vaccinations and to those patients who developed epileptic encephalopathy, severe myoclonic epilepsy, or Lennox-Gastaut syndrome, none of which apply to S.H. (*Id*. (citing Legido et al., *supra,* at Ex. 16).)

ii. Dr. Holmes' first supplemental report

In his second report, Dr. Holmes notes that despite the fact that treating physicians recorded the first events as seizures, S.H.'s presentation is nonetheless inconsistent with generalized seizures and that observations of treating physicians do not amount to diagnostic certainty. (Ex. C, pp. 1-2.) Further, Dr. Holmes contests that the diagnosis of epilepsy does not require simply two or more recurrent seizures, but two or more *unprovoked* seizures, which did not occur in S.H.'s case. (*Id*. at 2.) He notes that Dr. Kinsbourne incorrectly claims that because S.H.'s vaccinations triggered her first two seizures, and because her subsequent episodes were similar in nature to the first two, it follows that her subsequent episodes were also caused by her vaccinations. (*Id.*) According to Dr. Holmes, there are a "myriad of 'triggers'" for *seizures*; however, none of these triggers are said to cause *epilepsy.* (*Id.*) Finally, Dr. Holmes points out that the Uberall study cited by Dr. Kinsbourne lacked an appropriate control group and, to the extent that the study is informative, reported an "incredibly low" convulsion rate within 3 days of DTaP vaccination. (*Id.* at 3 (citing M.A. Uberall et al., *supra,* at (Ex. 25)).)

iii. Dr. Holmes' second supplemental report

Dr. Holmes' third report primarily addresses whether fever is part of the causal mechanism for post-vaccinal seizures. (Ex. D, p. 1.) He agrees that fever is triggered by pyrogens, which can be exogenous or endogenous, and that endogenous pyrogens include cytokines that are released by immune cells. (*Id.*) Dr. Holmes explains that, while these pyrogens act to increase body temperature, they also trigger receptors in the preoptic nucleus in the brain, which releases cytokines into the hypothalamus to set a new target temperature. (*Id.*) However, he disagrees that cytokines produced in the thigh following a DTaP vaccination can enter the brain in a manner and amount sufficient to produce a seizure. (*Id.*) Dr. Holmes writes that, in order for cytokines to activate central microglia, they need to cross the blood brain barrier, a regulatory interface in response to cytokines. (*Id.* at 2.) The amount of blood-borne cytokines crossing the blood brain barrier is "quite low," calculated at about .08% of the serum concentration. (*Id.* (citing W.A. Banks et al., *Human Interleukin (IL) 1α, Murin IL-1α and Murine IL-1β are Transported from Blood to Brain in the Mouse by a Shared Saturable Mechanism*, 259 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 988 (1991) (Ex. D, Tab 4)).) Studies have shown that there are limited pathways for the cytokines to travel past the blood brain barrier, and that these pathways only lead to specific areas, such as the hypothalamus, which are not known to generate seizures, and thus, the likelihood that cytokines generated in response to vaccination would cause a seizure is "miniscule." (*Id.* (citing Ning Quan, *In-Depth Conversation: Spectrum and Kinetics of Neuroimmune Afferent Pathways*, 40 BRAIN BEHAVIOR & IMMUNITY 1 (2014) (Ex. D, Tab 5)).) S.H. did not suffer from a fever after her immunization, which suggests that the immune response was not robust and makes it even less likely that her alleged seizures were immune-mediated. (*Id.*)

Dr. Holmes clarifies that cytokines are used by the central nervous system as neurotransmitters during central nervous system infection, trauma, and following seizures; however, the increase in cytokines associated with seizures is a response to the seizure, not the cause. (Ex. C, p. 2 (citing Gang Li et al., *Cytokines and Epilepsy*, 20 SEIZURE 249 (2011) (Ex. D, Tab 7)).) Dr. Holmes contends that Dr. Kinsbourne's reliance on the Dube study is misguided because the study utilized "very high, nonphysiologic doses" of IL-1β injected directly into the ventricles of the brain. (*Id.*) Dr. Holmes emphasizes that the amount of cytokines required to effectively lower the seizure threshold and generate afebrile seizures in the Dube study was more than 1000 times the amount recorded in humans following vaccination. (*Id.* (citing Dube et al., *supra,* at Ex. 48; Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT),* Haemophilus Influenzae *Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 HUM. VACCINES & IMMUNOTHERAPEUTICS 677 (2014) (Ex. D, Tab 13)).)

Dr. Holmes explains that most febrile seizures are generalized tonic-clonic seizures, while 30 to 35% have one or more of the following complex features: focal onset, lasting longer than 10 minutes, or multiple seizures during an illness episode. (Ex. D, p. 2.) One specific type of seizure, febrile status epilepticus, is characterized by

seizures lasting longer than 30 minutes and is the only type of seizure known to contribute to epilepsy. (*Id.* (citing Miquel Raspall-Chaure et al., *Outcome of Paediatric Convulsive Status Epilepticus: A Systematic Review*, 5 LANCET NEUROLOGY 769 (2006) (Ex. D, Tab 14)).) Dr. Holmes explains that "simple" and "complex" are only used to distinguish febrile seizures, which S.H. did not have. (*Id.* at 3 (citing Anne T. Berg et al., *Revised Terminology and Concepts for Organization of Seizures and Epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009*, 51 EPILEPSIA 676 (2010) (Ex. D, Tab 15)).) Dr. Holmes explains that S.H.'s medical records contain descriptions of symptoms consistent with generalized and focal seizures, and that in infants, seizures are usually consistent and manifest in the same way. (*Id.*) Thus, the variety of presentations, as well as the normal EEGs, suggest that S.H.'s episodes were not epileptic in nature. (*Id.*)

Dr. Holmes addresses Dr. Kinsbourne's reliance on studies of children with Dravet syndrome to suggest that children with especially low seizure thresholds may suffer afebrile seizures as a result of peripheral cytokine production following vaccination. (Ex. D, pp. 3-4.) Dr. Holmes suggests that if this were the case, then S.H.'s subsequent DTaP vaccinations would have also triggered seizures due to the fact that they elicit the same cytokine response argued to have caused S.H.'s seizures. (*Id.* at 4.) Further, there is no evidence that S.H. was in fact more susceptible to seizures. (*Id.*) Dr. Holmes suggests that the cited literature, which involves subjects with Dravet syndrome, with a SCN1A mutation, or who experienced febrile seizures, is not relevant in this case. (*Id.*)

Finally, Dr. Holmes submits that S.H.'s updated medical records do not suggest that she has epilepsy. (Ex. D, pp. 4-5.) Even if the events were seizures, Dr. Holmes indicates that they "did not cause any harm." (*Id.* at 4.)

iv. Dr. Holmes' third supplemental report

Dr. Holmes' final report notes that Dr. Kinsbourne's reliance on the Wise study is misguided due to the fact that it involved a passive reporting system of cases which "frequently defy facile assessment of whether vaccinations played a causal role since no information from non-vaccinated controls [are] included," as, without the control group, "it is impossible to say whether the vaccine increased the risk of convulsions" in this study's subjects. (Ex. G, p. 1 (citing Wise et al., *supra,* at Ex. 53).)

Dr. Holmes criticizes Dr. Kinsbourne's independent pathways theory as a misinterpretation and inappropriate extrapolation of the cited medical literature. (Ex. G, p. 2.) He further argues that there is no evidence that S.H. had a cytokine-induced inflammatory process that impacted the hypothalamic control center and hippocampal seizure generators. (*Id.*) He notes that S.H. did not have a fever or show any signs of seizure or epilepsy during objective testing. (*Id.*)

v. Testimony

To support his position that S.H. was experiencing some type of paroxysmal event, Dr. Holmes pointed to petitioner's observation of S.H. opening and closing her mouth during the episode as not being typically associated with generalized tonic-clonic seizures. (Tr. 89-90.) Instead, he suggested that tensing of the jaw and "twitching" of the mouth are generally observed. (*Id.* at 90.) He reiterated his concerns about S.H.'s 24-hour EEGs, which rendered normal results, before ultimately acknowledging that "a normal EEG does not rule out a seizure disorder." (*Id.* at 91.) Although he maintained that S.H.'s events were likely not seizures, Dr. Holmes conceded that, if the events were seizures, then S.H. had epilepsy, which he explained is quite common in children. (*Id.* at 87-94, 119-120.) He described a benign childhood epilepsy course that is commonly referred to as "smooth sailing epilepsy" where children respond well to medications, have a benign course, and have normal neural development and testing. (*Id.* at 119.) He acknowledged that placing S.H. on phenobarbital was a reasonable medical decision and agreed with Dr. Kinsbourne that S.H. was considered to be in remission of epilepsy when the phenobarbital was successfully discontinued. (*Id.* at 87, 117-24.) Dr. Holmes clarified that, prior to being taken off phenobarbital, S.H. was considered "under seizure control," and the medical community does not know for certain whether the medication is preventing further seizures. (*Id.* at 122-24.) The only indication of the efficacy of the medication is evidence that it is not working, *i.e.*, the child continues to have seizures while on medication. (*Id.* at 123.) For this reason, the decision to wean a child off anti-seizure medication is a clinical judgment that is based on the specific child's medical history and after "a long discussion" with the parents. (*Id.* at 124.)

Dr. Holmes testified that there is no evidence that the subject vaccines can cause afebrile seizures or that S.H. had an inherently low seizure threshold or compromised blood brain barrier prior to her initial seizures. (Tr. 96, 101.) He explained that the literature concerning Dravet syndrome is not relevant to this case as S.H. does not have Dravet syndrome and did not experience febrile seizures. (*Id.* at 97, 107-08.) Regarding Dr. Kinsbourne's assertion that seizures beget seizures, Dr. Holmes explained that there is no evidence to support this assertion and that the theory of kindling has been discarded by the medical community. (*Id.* at 98-100, 113-15, 124-25.) Dr. Holmes acknowledged that seizures can cause brain inflammation and the release of cytokines; however, he testified that there is no evidence that a few short seizures can increase cytokine production to the point of causing brain damage or a chronic seizure disorder. (*Id.* at 99-100, 103.)

Dr. Holmes clarified that a febrile seizure is caused by the fever itself. (Tr. 106-07.) Although he acknowledged that children are prone to febrile seizures at lower temperatures, he explained that fever requires a temperature of at least 100.4 degrees Fahrenheit. (*Id.* at 107, 110.) Thus, a child with temperature that is elevated but still lower than 100.4 degrees Fahrenheit when a seizure occurs is not experiencing a febrile seizure. (*Id.* at 107-08.) Dr. Holmes explained that vaccinations can trigger fever by releasing cytokines at the injection site that then travel up a signaling pathway to the hypothalamus. (*Id.* at 112.) The fever then activates neurons and opens ion channels,

leading to neuron depolarization and, ultimately, to seizure. (*Id.*) In S.H.'s case, there was no objective evidence of brain inflammation, as demonstrated by the test results or by the presence of fever, and no evidence that any brain inflammation lasted long enough to cause subsequent seizures. (*Id.* at 100-01.)

c. Respondent's Expert, Herman Staats, Ph.D. [16]

Respondent also filed expert reports from pathologist/immunologist Dr. Herman Staats. (Exs. E, H.) Dr. Staats provided additional testimony at the entitlement hearing. (Tr. 130-158.)

i. Dr. Staats' initial report[17]

Dr. Staats' outlines the innate and adaptive immune responses to vaccinations. (Ex. E, p. 2.) He explains that the innate immune response occurs rapidly, within minutes to hours after vaccinations, and is activated by exposure to vaccine adjuvants, such as alum, or pathogen components that activate conserved receptors in the immune system, such as toll-like receptors ("TLR"), that recognize pathogen-associated molecular patterns ("PAMPs") produced by microbes. (*Id.*) Cells of the innate immune system respond to PAMPs by secreting cytokines, which recruit other immune cells to the immunization site. (*Id*. (citing David Vermijlen & Immo Prinz, *Ontogeny of Innate T Lymphocytes – Some Innate Lymphocytes are More Innate Than Others*, 5 FRONTIERS IMMUNOLOGY, 1 (2014) (Ex. E, Tab 2); Karen Smith Korsholm et al., *T-Helper 1 and T-Helper 2 Adjuvants Induce Distinct Differences in the Magnitude, Quality and Kinetics of the Early Inflammatory Response at the Site of Injection*, 129 IMMUNOLOGY 75 (2009) (Ex. Ex, Tab 7); Isme De Kleer et al., *Ontonlogy of Myeloid Cells*, 5 FRONTIERS IMMUNOLOGY, 1 (2014) (Ex. E, Tab 6)).) These cytokine responses vary by vaccination but typically return to baseline levels within 1 to 7 days after vaccination. (*Id.* (citing William M. Gwinn et al., *A Comparison of Non-Toxic Vaccine Adjuvants for Their Ability to Enhance the Immunogenicity of Nasally-Administered Anthrax Recombinant Protective Antigen*, 31 VACCINE 1480 (2013) (Ex. E, Tab 10); Jacob T. Minang et al., *Enhanced Early Innate and T Cell-Mediated Responses in Subjects Immunized with*

[16] Dr. Staats received his bachelor's degree in medical technology from Salisbury University in 1988 and his PhD in microbiology and immunology from the University of South Alabama in 1992. (Ex. F, p. 1.) He has held nine different professorships in immunology and pathology since 1996 all at Duke University Medical Center. (*Id.*) He currently serves as Professor of Pathology, Associate Professor Immunology, and Associate Professor of Medicine at Duke University Medical Center. (*Id.*) Dr. Staats is certified as a medical technologist by the American Society of Clinical Pathologies. (*Id.* at 2.) He has served on the editorial board of six different medical journals from 1996 to 2017, and as a peer reviewer for 18 different journals since 1993. (*Id.* at 2-3.) Dr. Staats has served as primary or supporting author on 83 different pieces of peer-reviewed medical literature covering various topics of pathology and immunology. (*Id.* at 21-25; Tr. 131.)

[17] A significant portion of Dr. Staats's initial report addresses Dr. Kinsbourne's reliance on evidence pertaining to the whole cell pertussis vaccination and his assertion regarding reversion of pertussis toxin; however, because Dr. Kinsbourne effectively abandoned that reliance, it is not necessary to detail all of the evidence submitted to rebut it. (Ex. E, pp. 4-8.) Nonetheless, I have reviewed and considered all of the evidence pertaining to the whole cell pertussis vaccine that has been filed in this case.

Anthrax Vaccine Adsorbed Plus CPG 7909 (AV7909), 32 VACCINE 6847 (2014) (Ex. E, Tab 11); Korsholm et al., *supra,* at Ex. E, Tab 7; Jean-Paul M. Valensi Julia R. Carlson, & Gary A. Van Nest, *Systemic Cytokine Profiles in BALB/c Mice Immunized with Trivalent Influenza Vaccine Containing MF59 Oil Emulsion and Other Advanced Adjuvants*, 153 J. IMMUNOLOGY 4029 (1994) (Ex. E, Tab 1).)

Dr. Staats explains that, while Dr. Kinsbourne is correct to suggest that IL-1 is released following vaccination and that IL-1 may play a role in development of epilepsy, studies have shown that vaccinations do not *necessarily* induce elevated levels of IL-1β in alum-adjuvanted vaccines such as DTaP. (Ex. E, p. 5 (citing Valensi, Carlson, & Van Nest, *supra,* at Ex. E, Tab 1; Rachel Buglione-Corbett, Adjuvant-Specific Serum Cytokine Profiles in the Context of a DNA Prime-Protein Boost HIV-1 Vaccine: A Dissertation (April 29, 2013) (Ph.D dissertation, University of Massachusetts) (GSBS Dissertations and Theses) (Ex. E, Tab 43)).) For example, vaccine-induced IL-1β has been observed in mice that received HPV vaccines, such as Cervarix, which contains a combination of alum and TLR4 ligand MPL adjuvants, and Gardasil, which contains only alum adjuvants. (*Id.* at 6, (citing Tetsuo Nakayama, Yasuyo Kashiwagi, & Hisashi Kawashima, *Long-Term Regulation of Local Cytokine Production Following Immunization in Mice*, 62 MICROBIAL IMMUNOLOGY 124 (2018) (Ex. E, Tab 44)).) However, intramuscular injection of Gardasil revealed no increase in IL-1β. (*Id.* (citing Nakayama et al., *supra,* at Ex. E, Tab 44).) With regard to the effect on IL-1β induction and subsequent seizures triggered by both whole cell and acellular pertussis vaccines, studies demonstrate that the whole-cell pertussis vaccine has been associated with an increase in IL-1β, fever, and convulsions, while acellular pertussis "neither increased IL-1β nor induced behavioral changes in mice, but did induce the anti-inflammatory cytokine IL-10." (*Id.* (quoting Sheila Donnelly et al., *Whole-Cell but Not Acellular Pertussis Vaccines Induce Convulsive Activity in Mice: Evidence of a Role for Toxin-Induced Interleukin-1β in a New Murine Model for Analysis of Neuronal Side Effects of Vaccination*, 69 INFECTION & IMMUNITY 4217 (2001) (Ex. Ex, Tab 19)).) Providing further evidence against Dr. Kinsbourne's contention that S.H.'s DTaP vaccine induced IL-1β production that subsequently triggered her seizures, Dr. Staats cites his own study which used recombinant IL-1 as a vaccine adjuvant in mice. Using a nasal vaccine, which may provide direct access to the central nervous system, as well as intramuscular vaccines, they did not find any link between the use of IL-1 as an adjuvant and the induction of seizures. (*Id.* at 6-7 (citing William M. Gwinn et al., *Effective Induction of Protective Systemic Immunity with Nasally Administered Vaccines Adjuvanted with IL-1*, 28 VACCINE 6901 (2010) (Ex. E, Tab 45).)

Dr. Staats also discusses the timing of S.H.'s seizures as it relates to Dr. Kinsbourne's theory. (Ex. E, p. 7-8.) He explains that seizure onset within one hour of vaccination is not consistent with a vaccine-induced IL-1β triggered seizure. (*Id.* at 7.) Studies have shown that induction of a fever due to IL-1 took at least two hours in mouse studies and that the fever did not trigger any convulsion, thus it is unlikely that a DTaP vaccine could induce a seizure in under one hour. (*Id.* (citing Gwinn et al., *supra,* at Ex. E, Tab 45).) He further notes that, in clinical trials using infusion of recombinant IL-1, fever was not observed until 2-6 hours after infusion, and there were no reported

seizures. (*Id*. (citing Daniel Weisdorf et al., *Interluekin-1α Administered After Autologous Transplantation: A Phase I/II Clinical Trial*, 84 BLOOD 2044 (1994) (Ex. E, Tab 51)).) Dr. Staats contends that the timing of IL-1 induced fevers suggests that the timing of other IL-1 induced adverse events, such as seizures, would occur at the same time or later, but not sooner, "since IL-1-induced fever can be induced by IL-1 stimulation of the [central nervous system]." (*Id.* (citing Anders Blomqvist & David Engblom, *Neural Mechanisms of Inflammation-Induced Fever*, 24 NEUROSCIENTIST 381 (2018) (Ex. E, Tab 54)).) Finally, Dr. Staats explains that Dr. Kinsbourne relies on sources, such as Dube et al. and subsequent commentary, which focus entirely on the direct introduction of IL-1β to the brain, while vaccinations trigger cytokine responses in the periphery, two cases which operate very differently from one another. (*Id.* at 8.)

ii. Dr. Staats' supplemental report

Dr. Staats second report responds to specific comments made by Dr. Kinsbourne in his final report. (Ex. H.) First, he addresses Dr. Kinsbourne's revised opinion that S.H.'s seizures could be triggered either by the DTaP vaccine, Prevnar 13 vaccine, or both. (*Id.* at 1-2.) Dr. Staats explains that the Wise et al. study relied on by Dr. Kinsbourne notes that seizures were observed alongside Prevnar 13 vaccination, but the study was unable to identify anything beyond a temporal relationship and even explicitly noted that many of the reported events may be unrelated to the vaccine. (*Id.* (citing Wise et al., *supra,* at Ex. 53).)

Regarding Dr. Kinsbourne's reliance on publications from the Vezzani group to support his independent pathways theory, Dr. Staats points to one study, which stated, "[i]t is notable that cells in the hippocampus, a region contributing to the origin and spread of febrile seizures, synthesize IL-1β in response to fever or hyperthermia. Remarkably, IL-1β is not synthesized or released during other types of experimental seizures in the immature rodent . . . ." (*Id.* at 2 (quoting Vezzani & Baram, *supra,* at Ex. 22) (internal citations omitted).) Dr. Staats interprets this text to mean that the hippocampus produces IL-1β in response to fever, which then induces febrile seizures. (*Id.*) Further, the study indicates that IL-1β is not synthesized during other types of seizures, suggesting that afebrile seizures are not caused by inflammation, and thus, the study does not show that IL-1β can trigger afebrile seizures in the context of vaccine-induced inflammation. (*Id.*)

iii. Testimony

During the hearing, Dr. Staats explained that the more rapid innate immune response "takes some time to generate," with cytokine production tending to peak 3-6, and up to 12, hours after vaccination, while the adaptive immune response can take upwards of a week or more. (Tr. 134-38.) Dr. Staats testified that the alleged timeframe in this case (*i.e*. one hour or less) does not align with the general understanding of vaccine-induced inflammatory cytokine responses. (*Id.* at 144.) He explained that the earliest he has observed fever following vaccination where IL-1 was used as an adjuvant was 2 hours, peaking at 2-6 hours, post-vaccination. (*Id.* at 136-

37.) Even after direct exposure with IL-1, fever was still not observed until 2 hours after vaccination. (*Id.* at 137.) Dr. Staats suggested that the post-vaccination inflammatory process may take longer where IL-1 is not directly administered. (*Id.* at 137-38.) Dr. Staats testified that his expectation would be that vaccine-induced inflammation leading to seizure would take at least two hours, or until after onset of fever, as fever is an indicator of excessive systemic inflammation. (*Id.* at 140.) In fact, he indicated that most of the literature he encountered on this topic of cytokine response to vaccination involved fever as the adverse event. (*Id.* at 142.) He disclaimed the relevance of any studies involving direct injection into the brain as this method allows for bypass of the fever control center of the brain and entry into the seizure control portion of the brain. (*Id.* at 141-42, 155.)

However, on cross-examination, Dr. Staats acknowledged that the studies he relied upon to determine the reasonableness of the alleged timeframe did not measure temperature at 20 minutes, 30 minutes, or 1 hour after vaccination. (Tr. 147, 149-50.) He opined that the studies involving human trials provide stronger evidence as infusion took place in the hospital where participants were continuously monitored. (*Id.* at 156.) In response to the undersigned's questioning, Dr. Staats clarified the relevance of some of the studies cited in his own expert report. (*Id.* at 152-53.) He explained that vaccines may induce an array of proinflammatory cytokines after vaccination, and the array may not necessarily include IL-1. (*Id.* at 153-54.) Without measuring the cytokine response in the particular individual, Dr. Staats could not say whether IL-1 was induced following S.H.'s vaccinations, but studies examining IL-1β have generally shown it is not one of the earlier cytokines to develop post-vaccination. (*Id.* at 154-55.)

V. Analysis

a. Diagnosis

The parties have offered conflicting opinions regarding whether the convulsive events that S.H. experienced in May of 2015 were in fact seizures. Where the existence and nature of the injury itself is in dispute, the Federal Circuit has concluded that it is the duty of the special master "to first determine what injury, if any, [is] supported by the evidence presented in the record before applying the *Althen* test to determine causation." *Lombardi v. Sec'y of Health & Human Servs.*, 656 F.3d 1343, 1352-53 (Fed. Cir. 2001) (citing *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339 (Fed. Cir. 2010)).

At the hearing, Dr. Holmes suggested, on respondent's behalf, that the events that S.H. experienced in May of 2015 were actually "paroxysmal events," which mimic seizures but lack the postictal period that usually follows a generalized tonic-clonic seizure. (Tr. 87-92; *see also* Ex. A, p. 11 (citing Obeid & Mikati, *supra,* at Ex. A, Tab 1).) Dr. Holmes indicated that many paroxysmal events "have only been recently described or are only now being increasingly recognized." (Ex. A, p. 11.) Obeid & Mikati further recognize that diagnosis is challenging due to the limited repertoire of both epileptic and nonepileptic paroxysmal clinical manifestations. (Obeid & Mikati, *supra,* at

Ex. A, Tab 1, p. 1.) Differentiating between nonepileptic and epileptic events mainly relies on awareness of different mimickers of epilepsy and "the art of history-taking." (*Id.*) Dr. Holmes appeared to characterize paroxysmal events as a catch-all term. He opined that "everything that shakes is not a seizure" and listed several different conditions that involve convulsions without seizures, though he acknowledged he could not identify a specific term that captures S.H.'s convulsions. (Tr. 88-89.) Dr. Holmes further acknowledged it is difficult to distinguish seizures and paroxysmal events. (*Id*. at 89.)

Dr. Holmes noted that S.H.'s "lip-smacking" is not typical as the jaw generally tenses and the mouth twitches during seizing, and that it is unusual for a child to cry out after a seizure. (Tr. at 89-90.) Dr. Holmes further pointed to S.H.'s normal MRI, EEG, and CT scan to bolster his evaluation of these events. (*Id.* at 91-92.) Though he acknowledged that a normal EEG does not rule out the possibility of a seizure disorder, Dr. Holmes opined that the absence of interictal abnormalities on both 24-hour EEGs indicates a "pretty high" likelihood that S.H. was not experiencing active seizure disorder. (*Id.* at 91.) However, during the hearing he qualified his opinion by stating, "I cannot say, you know, [with] 100 percent confidence" that S.H. did not experience seizures and noting in particular that "the mother's story today was compelling for a number of reasons for seizures." (Tr. 87.) Further, Dr. Holmes agreed that, if the May 22 events were seizures, then the following May 26 and May 28 events were also likely seizures. (*Id.* at 115-16.) He further agreed with Dr. Kinsbourne that, if the events were considered seizures, then S.H. would meet the definition of "epilepsy" because she would have had two or more unprovoked seizures. (*Id.* at 93.) In fact, when noting the difficulty in distinguishing seizures and paroxysmal events, Dr. Holmes noted that S.H.'s events "could well have been epileptic seizures." (Tr. 89.)

I find the medical records preponderately establish that the events S.H. experienced in May of 2015 were seizures. While respondent is correct in noting that the medical records could be interpreted as expressing doubt as to whether petitioner was experiencing active seizure disorder, S.H. was consistently assessed as experiencing seizures, including assessments based on firsthand observation by the treating physicians. (Ex. 6, p. 6 (Dr. Cha's comment that S.H. presented with "generalized seizures after receiving immunizations" on 5/22/2015); *id.* at 8-9 (ED transfer note with recurrent seizures impression by Dr. Shook on 5/22/2015); *id.* at 20 (noting that Dr. Shook "witnessed seizure activity" on 5/22/2015); *id.* at 52-53 (ED transfer note with seizure diagnosis by Dr. Tung on 5/26/2023); *id.* at 109-10 (ED transfer note with recurrent seizure diagnosis by Dr. Tung on 5/28/2015); Ex. 4, pp. 10-12 (assessment of seizure with provoking factor by Dr. Bose on 5/23/2015); *id.* at 13-14 (single seizure assessment by Dr. Marzo on 5/23/2015); *id.* at 83 (impression of provoked seizures by Dr. Bose on 5/27/2015).) By May 27, 2015, S.H.'s treating physicians were assessing her condition as epilepsy. (Ex. 4, 78 (assessment of "absence epilepsy" by Dr. Fuqua on 5/27/2023); *id.* at 152-53 (epilepsy assessment by Dr. Chinnici on 5/28/2015); *id.* at 157 (epilepsy assessment by Dr. Bose on 5/29/2015)). In fact, Dr. Fuque was the sole treating physician that expressed some doubt, commenting that her "spells . . . may or may not be seizures" because petitioner did not

report a postictal period. (Ex. 4, p. 79.) However, Dr. Fugue's principal assessment was absence epilepsy, which is not consistent with Dr. Holmes's opinion regarding nonepileptic paroxysmal events.[18] (*Id.* at 78.) In the longer term, S.H.'s physicians treated her with phenobarbital, an anti-seizure medication. (*Id.* at 154-61, 170-71.) Dr. Holmes explained that he agreed with the decision to treat S.H. with phenobarbital because Dr. Bose likely believed that the events were recurrent seizures based on S.H.'s history and wanted to prevent further events. (Tr. 117, 120.)

Under the Vaccine Act, special masters must consider, but are not bound by, "any diagnosis, conclusion [or] medical judgment . . . which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, . . . injury, [or] condition." § 300aa-13(b)(1); *see also Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993) (recognizing that medical records generally "warrant consideration as trustworthy evidence"). Special masters have "discretion to determine the relative weight of evidence presented, including contemporaneous medical records and oral testimony." *Caron ex rel. A.C. v. Sec'y of Health & Human Servs.*, 136 Fed. Cl. 360, 376 (2018). In the instant case, the record reflects a contemporaneous medical judgment that S.H.'s events were seizures. I have considered Dr. Holmes's additional opinion regarding paroxysmal events; however, it contains at least some equivocation and does not outweigh the contemporaneous medical judgments of the treating physicians. Even having reached a different conclusion, Dr. Holmes was careful to note that he was not present for these events and was not criticizing the treating physicians for deciding to treat these events as seizures. Accordingly, I find that petitioner has preponderantly shown that S.H. suffered seizures in May of 2015.

b. Severity Threshold

In order to state a claim for a vaccine-related injury under the Vaccine Act, a vaccinee must have either:

> (i) suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine, or (ii) died from the administration of the vaccine, or (iii) suffered such illness, disability, injury or condition from the vaccine which resulted in inpatient hospitalization and surgical intervention.

§ 300aa-11(c)(1)(D).

[18] Absence epilepsy is characterized by absence seizures. *Absence Epilepsy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=73435 (last visited Aug. 28, 2023). Absence seizures consist of sudden momentary breaks in consciousness of thought or activity and are sometimes accompanied by clonic movements, especially in the eyelids. *Absence Seizure*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=105397 (last visited Aug. 28, 2023).

In this case, petitioner raised several separate allegations in her petition as to why she has satisfied this requirement. First, she alleged that S.H. underwent a lumbar puncture during her hospitalization that constitutes a surgical intervention. (ECF No. 1, p. 4.) Second, she alleged that S.H. suffered a speech delay resulting from her phenobarbital treatment that constitutes a residual effect or complication that persisted for more than six months. (*Id*.) Third, she alleged that the need for an extended course of phenobarbital itself constitutes a complication or residual effect of S.H.'s condition. (*Id*.) By the time of her prehearing brief, petitioner had narrowed her argument to the third of these contentions – that treatment with phenobarbital itself is sufficient to satisfy the severity requirement. (ECF No. 81, pp. 22-23.) Because I agree with petitioner's narrower argument, it is not necessary to address the other contentions.

In *Wright v. Secretary of Health & Human Services*, the Federal Circuit interpreted the Vaccine Act's six-month severity provision to require a showing that the "residual effects" of the vaccine injury were detrimental conditions, such as lingering or recurring signs and symptoms of the vaccine injury. 22 F.4th 999, 1004-07 (Fed. Cir. 2022). As a result, the Federal Circuit held that B.W.'s testing for a possible recurrence of thrombocytopenic purpura did not meet the Vaccine Act's requirements because the test revealed that there were no lingering symptoms or recurrence of the vaccine injury, and there was no showing or argument that the testing was detrimental to B.W.'s health. *Id.* at 1006. Additionally, B.W.'s "relatively non-invasive ongoing monitoring" itself did not amount to an "ongoing disability" from his vaccine nor was it indicative that he "suffered" or was "seriously injured" as there were no "lingering somatic effects at all after six months." *Id.* at 1007. Respondent argues that taking medication without any apparent side effects, such as phenobarbital at issue in this case, is far less intrusive and painful than even the testing and monitoring examined in *Wright*. (ECF No. 79, p. 18-19.)

However, citing two prior decision by special masters, the *Wright* court specified that the decision did not disturb existing case law holding that a course of treatment lasting longer than six months may be considered a "residual effect" within the meaning of the Vaccine Act. 22 F.4th at 1007 (citing *H.S. v. Sec'y of Health & Human Servs.*, No. 14-1057V, 2015 WL 1588366 (Fed. Cl. Spec. Mstr. Mar. 13, 2015); *Faup v. Sec'y of Health & Human Servs.*, No. 12-87V, 2015 WL 443802 (Fed. Cl. Spec. Mstr. Jan. 13, 2015)). The Federal Circuit explained,

> During a long course of treatment, the patient generally has some lingering condition such that symptoms will likely recur if the treatment were stopped. Otherwise, the long course of treatment would not be necessary.
>
> We do not decide today whether a course of testing or monitoring that is part of the management or treatment of a condition, necessary even in the absence of possible symptoms, could be a "residual effect." In such a case, the monitoring may be considered part of the treatment of a condition that has not resolved, if the patient's somatic condition increases the risk of recurrence.

Id.

In *H.S. v. Secretary of Health & Human Services*, the special master found that H.S. suffered the residual effects of a skull fracture for longer than six months, despite only wearing a neck collar for about 12 weeks, because H.S.'s treating physicians restricted his activity for an additional year, indicating a medical judgment that H.S. remained in a vulnerable state and the injury had not fully resolved despite the lack of outward symptoms. 2015 WL 1588366, at *2-3. In *Faup v. Secretary of Health & Humans Services*, the experts agreed that A.F. was not exhibiting symptoms of juvenile idiopathic arthritis for more than six months after vaccination at least in part because she was medicated with Methotrexate to prevent the occurrence of those symptoms. 2015 WL 443802, at *4. While recognizing the necessity of Methotrexate to control A.F.'s symptoms and prevent permanent joint damage, the experts explained that they did not know whether such treatment "has anything to do with the achievement of remission" but most doctors agreed that "judicious use of a medication like Methotrexate is necessary simply because we do not know who, at disease onset, is earmarked to follow a more or less favorable course." *Id.* Accordingly, the special master found that A.F.'s ongoing need for medication was a residual effect or complication of her vaccine injury that lasted longer than six months. *Id.* Both *H.S*. and *Faup* stand for the proposition, as stated by the special master in *Faup*, that "'residual effects or complications' and 'symptomatic' are not synonymous; one can suffer from a disease without exhibiting any clinical signs thereof." *Id*.

Faup and *H.S*. contrast with a prior decision that noted that increased risk of recurrence alone is insufficient to constitute a residual effect or complication within the meaning of the Vaccine Act. *Parsley v. Sec'y of Health & Human Servs*., No. 08-718V, 2011 WL 2463539, at *5 (Fed. Cl. Spec. Mstr. May 27, 2011). Additionally, in a much earlier case highlighted by respondent, a special master concluded, on facts very similar to this case, that an extended course of phenobarbital did not constitute evidence of complications or residual effects under the statute. *Toebe v. Sec'y of Health & Human Servs.*, No. 91-1623V, 1992 WL 101638 (Fed. Cl. Spec. Mstr. Apr. 23, 1992). The child in *Toebe* experienced a series of afebrile seizures within hours of her DTaP vaccination, requiring an extended course of phenobarbital that was maintained for approximately 28 months with consistently normal EEGs and without any further events. *Id.* at *1. The *Toebe* petitioner argued that the course of phenobarbital and the treating physician's impression of seizure disorder was sufficient evidence to show that the child suffered the residual effects or complications of the seizure disorder for more than six months. *Id.* at *3. However, despite being placed on an extended course of phenobarbital and experiencing some transient side effects from the medication and periodic testing, the special master found that the child in *Toebe* had "no lasting measurable sequela," reasoning that a finding that phenobarbital blocked seizure activity would be speculative without evidence of seizure activity after discontinuation of the medication. *Id.*

In this case, both parties' experts explained that a child is not considered to have achieved "remission" of epilepsy until after she has been successfully weaned from anti-

seizure medication such as phenobarbital. (Tr. 33, 122-23.) Up until that point, a child who is on anti-seizure medication and not experiencing seizures is considered "under seizure control" rather than in remission. (*Id.* at 122.) As Dr. Holmes explained, anti-seizure medications, such as phenobarbital, "don't cure epilepsy," they only prevent seizures from manifesting. (*Id.* at 120.) Thus, S.H. did not obtain her epilepsy remission status until the phenobarbital was discontinued and she did not thereafter have another seizure. This did not occur until more than six months post-vaccination. While respondent is correct that "S.H. was unquestionably symptom-free within six months of vaccination" (ECF No. 79, p. 18.), Dr. Holmes explained that it is impossible to know whether there has been resolution of the seizure threshold or whether control of the seizures is due to medication. (Tr. at 122.) Both parties' experts testified to the medical community's general understanding that a child may remain on anti-seizure medication for an extended period both due to the risk of recurrence and in order to give the brain time to become less excitable. (*Id.* at 52-53, 117-20.) Dr. Holmes specifically confirmed that brain excitability remains an ongoing condition even while administering phenobarbital to prevent seizures. (*Id*. at 120-21.)

Respondent stresses a notation in the medical records indicating that S.H.'s parents preferred to continue the phenobarbital until after S.H.'s 12-month immunizations, stating that S.H.'s treating physicians "apparently did not require her to take Phenobarbital for as long as she did." (ECF No. 79, pp. 18-19 (citing Ex. 5, p. 228).) However, Dr. Holmes explained that the decision to discontinue anti-seizure medication is not a rote decision but an assessment that is made on a case-by-case basis and informed by specific clinical history. (Tr. 123-24.) Dr. Holmes thoroughly explained that the decision to wean a child off medication is one that is made after a "long discussion" with the parents about the pros and cons of discontinuing medication in light of the fact that doctors do not know whether a patient is truly in remission until after the medication is discontinued. (*Id.* at 123-24.) It is always a "tough question" due to the lack of certainty. (*Id.*) When I asked Dr. Holmes if the decision to discontinue phenobarbital is a case-specific clinical judgment, he answered, "[t]hat's absolutely correct." (*Id.* at 124.) Even having cited factors that left S.H.'s own condition less concerning, Dr. Holmes did not criticize the decision to keep S.H. on phenobarbital through her 12-month vaccinations and wean her off the medications after those vaccinations if there were no subsequent events. (*Id.* at 117-18.) He characterized it as "proactive," but did not suggest it was unreasonable or beyond normal clinical judgment. In fact, he suggested the timing of S.H.s' initial weaning was "appropriate" and a "reasonable option here . . . waiting for time so the brain becomes less excitable." (*Id.* at 118, 120.)[19]

[19] In any event, specifically asked at what point S.H.'s phenobarbital level would become subtherapeutic, petitioner's treating physician expected that it would take "up to 12 weeks for the phenobarbital level to drop." (Ex. 5, p. 307.) Therefore, even if S.H. had been weaned off her medication beginning at her appointment on October 6, 2015, as originally recommended by her treating physicians, they would not have considered her sub-therapeutic until December 29, 2015, which would also be six months after her onset of May 22, 2015, when she had her first seizure. Arguably then, the prolonging of the phenobarbital beyond the 12-month immunizations does not actually change the analysis.

In light of all of this, I conclude that this case is in line with *Faup* and *H.S.* given that S.H.'s course of phenobarbital evidences a medical judgment based on S.H.'s own clinical history that she "remained in a vulnerable state and had not returned to [her] pre-vaccination condition of health" despite an absence of outward symptoms. *H.S.*, 2015 WL 1588366, at *3. Although *Toebe* reached a different conclusion on similar facts, *Toebe* was resolved on a motion to dismiss without expert testimony regarding the medical community's understanding of the difference between seizure control and remission or the considerations that go into determining when to conclude a given patient's anti-seizure treatment.[20] 1992 WL 101638.

In light of all of the above, I find that petitioner has satisfied the six-month severity requirement by virtue of S.H.'s extended course of phenobarbital.[21]

c. *Althen* Prong One

Under the first *Althen* prong, petitioner must provide preponderant evidence of a medical theory causally connecting the subject vaccination with the alleged injury. *Althen v. Sec'y of Health & Human Servs.*, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). Petitioner's theory must be "legally probable" but need not be "medically or scientifically certain." *Knudsen ex rel. Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Moreover, petitioner is neither required to submit medical literature or epidemiological studies nor to demonstrate a specific mechanism or a generally accepted medical theory to meet her burden under *Althen* prong one. *Morris v. Sec'y of Health & Human Servs.*, No. 19-1750V, 2023 WL 5092691, at *6 (Fed. Cl. Spec. Mstr. July 11, 2023) (citing *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009)). However, petitioner's theory "must be supported by a sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548 (citations omitted).

It has been recognized in other cases that a vaccine can cause seizures in some contexts, such as where a vaccinee has some genetic abnormality or where seizures are febrile.[22] For example, in this case respondent's expert, Dr. Holmes, agrees that

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[20] Of course, rulings and decisions of other special masters are not binding. *See Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1358 (Fed. Cir. 2019). However, special masters are encouraged to draw upon their accumulated experience assessing Vaccine Act claims when judging the merits of individual claims. *See Tenneson v. Sec'y of Health & Human Servs.*, 142 Fed. Cl. 329, 340 (2019); *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993). As the Chief Special Master has suggested, special masters would "be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions." *Simeone ex rel. R.S. v. Sec'y of Health & Human Servs.*, No. 20-1375V, 2023 WL 5286292, at *7 n.7 (Fed. Cl. Spec. Mstr. Feb. 24, 2023).

[21] This conclusion is closely related to my conclusion that S.H. did suffer epilepsy as discussed in the preceding section. If S.H. was not experiencing seizures, then this would raise additional questions with respect to the role of phenobarbital in her treatment. (Tr. 126-29.)

[22] *See, e.g.*, *Sharpe v. Sec'y of Health & Human Servs.*, No. 14-65V, 2021 WL 1291720, at *7-9 (Fed. Cl. Spec. Mstr. Feb. 19, 2021) (concluding that the petitioner had sufficiently shown that the DTaP vaccine

vaccination can trigger febrile seizures. (Tr. 111.) However, Dr. Kinsbourne proposes that two vaccinations, but principally the acellular pertussis-containing DTaP vaccine, caused *afebrile* seizures without any established genetic susceptibility. (Ex. 7, p. 3.) This represents a separate context in which numerous prior petitioners have not been successful.[23]

Initially, Dr. Kinsbourne asserted that there is epidemiologic support for the idea that vaccines can cause seizures, necessarily including afebrile seizures (Ex. 7, p. 3); however, once pressed with respect to the DTaP vaccine, he later acknowledged that

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caused-in-fact the significant aggravation of L.M.'s preexisting seizure disorder that was associated in some part with an underlying genetic mutation); *Ginn v. Sec'y of Health & Human Servs.*, No. 16-1466V, 2021 WL 1558342, at *5-7 (Fed. Cl. Spec. Mstr. Mar. 26, 2021) (concluding that vaccines can cause febrile seizure that can in turn lead to epilepsy); *Fuller ex rel. B.F.*, 2019 WL 7576382, at *14-16 (finding that petitioner preponderantly established that the DTaP vaccine can cause complex febrile seizures); *see also Thompson v. Sec'y of Health & Human Servs.*, No. 15-671V, 2023 WL 21234, at *23-26 (Fed. Cl. Spec. Mstr. Jan. 3, 2023) (concluding that petitioner had preponderantly shown that the Pentacel vaccine, which includes DTaP, significantly aggravated an underlying and previously asymptomatic Dravet syndrome). *But see Osenbach v. Sec'y of Health & Human Servs.*, No. 16-419V, 2023 WL 5714809, at *25-26 (Fed. Cl. Spec. Mstr. Aug. 8, 2023) (distinguishing *Sharpe* and *Ginn* and citing several cases where petitioners have been unsuccessful in proving causation where a child's seizure was presumably vaccine-induced but where the child was later determined to have Dravet syndrome), *motion for review filed* (Fed. Cl. Sept. 7, 2023).

[23] *Borin ex rel. Borin v. Sec'y of Health & Human Servs.*, No. 99-491V, 2003 WL 21439673, at *11 (Fed. Cl. Spec. Mstr. May 29, 2003) (finding that it is not plausible "that DPT would, in the absence of acute encephalopathy and/or fever, cause brief seizures when the child is otherwise normal"); *Nanez v. Sec'y of Health & Human Servs.*, No. 20-1261V, 2003 WL 22434113, at *3-4 (Fed. Cl. Spec. Mstr. Sept. 23, 2003) (concluding that petitioners had not presented a credible prima facie case showing that the acellular pertussis vaccine caused their child's afebrile seizures); *K.L. v. Sec'y of Health & Human Servs.*, No. 12-312V, 2017 WL 1713110, at *14-16 (Fed. Cl. Spec. Mstr. Mar. 17, 2017) (finding that petitioner had not sufficiently shown that the HPV vaccine can cause afebrile seizures), *aff'd*, 134 Fed. Cl. 579 (2017); *Caredio ex rel. D.C. v. Sec'y of Health & Human Servs.*, No. 17-0079V, 2021 WL 4100294, at *30-34 (Fed. Cl. Spec. Mstr. July 30, 2021) (rejecting petitioner's medical theory that a molecular-mimicry driven cross-reaction instigated by the flu vaccine caused afebrile seizures, eventually evolving into an autoimmune form of epilepsy or epilespia partializ continua), *aff'd*, 2021 WL 6058835 (Fed. Cl. Dec. 3, 2021); *Chavez v. Sec'y of Health & Human Servs.*, No. 16-1479V, 2022 WL 3368502, at *23-25 (Fed. Cl. Spec. Mstr. July 19, 2022) (finding petitioner's medical theory, which proposed that adjuvants in the Pediarix, pneumococcal conjugate, *haemophilus influenzae* type B, and rotavirus vaccines provoked the production of proinflammatory cytokines and caused afebrile seizures, was not sound and reliable); *Gram ex rel. A.L.M. v. Sec'y of Health & Human Servs.*, No. 15-515V, 2022 WL 17687972, at *41-47 (Fed. Cl. Spec. Mstr. Nov. 16, 2022) (finding as unpersuasive petitioner's theory that an IL-1β mediated response to MMR vaccination can trigger afebrile seizures and explaining that "there is no convincing evidence that vaccine can cause seizures in the absence of a fever"); *Walters v. Sec'y of Health & Human Servs.*, No. 15-1380V, 2023 WL 3750716, at *32 (Fed. Cl. Spec. Mstr. June 1, 2023) (concluding that petitioner had not provided preponderant evidence showing that the DTaP vaccine can cause, in pertinent part, afebrile seizure activity), *aff'd*, 2023 WL 5274006 (Fed. Cl. July 31, 2023), *appeal docketed*, No. 23-2369 (Fed. Cir. Sept. 8, 2023); *Hargrove ex rel. A.F.M. v. Sec'y of Health & Human Servs.*, No. 17-233V, 2023 WL 8071917, at *33-36 (Fed. Cl. Spec. Mstr. Oct. 27, 2023) (finding that petitioner had not proven that afebrile seizures can be caused by DTaP vaccination through a cytokine driven process); *Bechel v. Sec'y of Health & Human Servs.*, No. 16-887V, 2023 WL 8588184 (Fed. Cl. Spec. Mstr. May 22, 2023) (determining that petitioners did not carry their burden of showing that the MMR or DTaP vaccines can cause afebrile seizures), *aff'd* (Fed. Cl. Nov. 20, 2023).

he could not locate any epidemiologic evidence that compared incidences of afebrile seizures following DTaP vaccinations against background rates or controls and that he ultimately is "not in a position to rely on epidemiological evidence on this issue."[24] (Ex. 28, p. 4). He later attempted to reverse course, adding assertions with respect to the Prevnar 13 vaccine and suggesting during the hearing that there is "some epidemiological backing" for his theory. (Tr. 35-36.) However, the additional literature he cited again centers on an association between *febrile* seizures and vaccination. (*Id.* 35-37 (citing Sun et al., *supra,* at Ex. 21).) Importantly, and contrary to Dr. Kinsbourne's competing opinion, Dr. Holmes explained that in febrile seizures the fever itself causes the seizure. (*Id.* at 106-07, 111-13.) Given the accepted connection between fever and seizure on the one hand, and vaccination and fever on the other, Dr. Kinsbourne has not shown that it would be reasonable to rely on statistical findings that include post-vaccination febrile seizure as evidence that the subject vaccines can cause seizures in the absence of a seizure-causing fever. Rather, he acknowledged in his testimony that vaccine-induced afebrile seizures are rare enough to go undetected in epidemiological studies.[25] (*Id.* at 35-36.)

Dr. Kinsbourne alternatively sought to rely on literature pertaining to afebrile seizures in those with Dravet syndrome. (Ex. 28, pp. 4-6 (citing Francesca Ragona et al., *Dravet Syndrome: Early Clinical Manifestations and Cognitive Outcome in 37 Italian Patients*, 32 BRAIN & DEV. 71 (2010) (Ex. 39); Berg et al., *supra,* at Ex. 29; Ingrid E. Scheffer, Commentary, *Vaccination Triggers, Rather Than Causes, Seizures*, 15 EPILEPSY CURRENTS 335 (2015) (Ex. 40); Fernando Cendes & Raman Sankar, *Vaccinations and Febrile Seizures*, 52 EPILEPSIA 23 (2011) (Ex. 31)).) However, he likewise failed to substantiate how epidemiology concerning afebrile seizures following

[24] In his initial report, Dr. Kinsbourne additionally opined that the toxoided pertussis toxin in the acellular pertussis vaccine can spontaneously revert to toxin, causing similar consequences as the older formulations of the whole cell pertussis vaccine. (Ex. 7, p. 3.) However, Dr. Kinsbourne could not substantiate this theory. As pointed out by Dr. Staats, the two manuscripts that Dr. Kinsbourne provided in support of his spontaneous reversion theory simply discuss safety measures, *e.g.*, ensuring that the toxoided pertussis does not revert to active pertussis, taken by vaccine producers before regulatory approval of the vaccines. (Ex. E, p. 4.) I have previously discussed the many cases that persuasively explain why studies relating to the safety of the whole cell pertussis vaccine are not applicable to the acellular pertussis vaccine. *See, e.g.*, *Kottenstette*, 2020 WL 4197301, at *8-10; *Bangerter ex rel. D.B.*, 2022 WL 439535, at *22-23. Dr. Kinsbourne ultimately disavowed his spontaneous reversion theory, stating that he was unable to locate any further literature in support of his theory. (Tr. 65.) He thus abandoned his intimation that any propensity of the whole cell pertussis vaccine to cause seizures should inform interpretation of epidemiology relating to the acellular pertussis vaccine.

[25] I do acknowledge that, per Dr. Kinsbourne's opinion, fever is a concomitant rather than necessarily causal feature of febrile seizures. (Ex. 28, pp. 1-2.) Accordingly, one could argue that under Dr. Kinsbourne's rationale the epidemiologic data should be interpreted without distinguishing between febrile and afebrile seizures. For all the reasons discussed herein, however, I am not persuaded by Dr. Kinsbourne's theory. In any event, even if Dr. Kinsbourne's theory that there are multiple pathways for cytokines to cause seizures were persuasive, this would not automatically refute that fevers themselves can cause seizures in at least some cases, as Dr. Holmes has opined. Accordingly, the inclusion of febrile seizures in the data would still complicate Kinsbourne's reliance on that data with respect to afebrile seizures. Ultimately, while noting these points in the interest of completeness, it is up to petitioner and Dr. Kinsbourne to establish the relevance of the epidemiology they would seek to rely upon and they have not done so.

vaccination of children with Dravet syndrome, a condition of which S.H. does not suffer, is analogous to this case, especially where his premise that S.H. had a low seizure threshold represents conjecture unsupported by record evidence. (Tr. 42-44, 62.) As Dr. Holmes explained, Dravet syndrome is a condition in which a sodium channel mutation results in epilepsy. (*Id.* at 95.) Even if a vaccine causes a seizure in a Dravet syndrome patient, the vaccine did not cause the epilepsy, the Dravet syndrome did. (*Id.*) And even in that context, where there may be many things that can provoke a seizure in a predisposed individual, temperature still appears to be the primary culprit in seizure activity. (*Id.* at 111.) By contrast, Dr. Kinsbourne acknowledged during the hearing that he has no basis to explain why S.H. purportedly had an unusually low seizure threshold at the time of seizure onset; he simply concludes that she did "for whatever reason – we don't know." (*Id.* at 43; *but see id.* at 96 (Dr. Holmes opining S.H. did not have a lowered seizure threshold).) In any event, Dr. Kinsbourne's suggestion that findings relative to Dravet syndrome can be meaningfully applied outside of the context of that very specific vulnerability is Dr. Kinsbourne's conjecture alone. (*Id.* at 97 (Dr. Holmes refuting Dr. Kinsbourne's reliance on Dravet syndrome literature).)

Of course, petitioner need not present epidemiologic studies to meet her burden of proof under *Althen* prong one. *Andreu*, 569 F.3d at 1378. In that regard, Dr. Kinsbourne also presented a separate theory of causation. Dr. Kinsbourne explains that vaccination causes the release of proinflammatory cytokines, including IL-1β. (Ex. 7, p. 3 (citing Chen, Howard, & Oppenheim, *supra,* at Ex. 10)).) He further observes that IL-1β in turn can cause or contribute to fever while also having a "well-documented propensity to cause seizures." (*Id.* (citing Vezzani & Baram, *supra,* at Ex. 22; Sanon, Desgent, Carmant, *supra,* at Ex. 19).) Dr. Kinsbourne indicates that the presence of fever is not required for IL-1β to lead to seizures. (Ex. 28, p. 2 (citing Dube et al., *supra,* at Ex. 48; Mazarati et al., *supra,* at Ex. 33; Vezzani & Baram, *supra,* at Ex. 22).) In particular, he stresses that a study by Dube et al. found that high doses of IL-1β can provoke seizures "without increased brain temperature." (*Id.* (quoting Dube et al., *supra,* at Ex. 48, pp. 3-4).) Dr. Kinsbourne thus contends that IL-1β has been shown to induce seizures by a pathway independent of the pathway by which a release of cytokines can cause fever. (Ex. 45, p. 4.) Specifically, Dr. Kinsbourne submits that "the flow of cytokines to the hypothalamic control center for temperature and the flow of cytokines to the hippocampal and neocortical seizure generators are independent of each other." (*Id.*; *see also* Tr. 39.) There is no dispute that the papers cited by Dr. Kinsbourne *hypothesize* multiple pathways by which IL-1β could cause seizures (Tr. 157 (Dr. Staats acknowledging that the Dube articles "proposes" two different pathways)); however, respondent's experts raise several points that diminish the value of this hypothesis.

Dr. Holmes cautions that it is unlikely that cytokines produced peripherally by vaccination would be able to traffic across the blood brain barrier without also producing other consequences, such as fever. (Tr. 101, 112-13; Ex. D, pp. 1-2.) Even Dr. Kinsbourne's own use of the term "concomitant" to describe his understanding of the relationship between fevers and seizures implies as much, even as he urges that the two events manifest by independent pathways. (Ex. 45, p. 5.) Although Dr. Holmes

agrees that cytokines can produce endogenous fever, he indicates that the relevant literature establishes that the increase in cytokines associated with seizures is a response to the seizure, not its cause. (Ex. D, pp. 1-2 (citing Li et al., *supra,* at Ex. D, Tab 7).) For example, Dr. Holmes cites a review paper that looks at some of the same research as cited by Dr. Kinsbourne, as well as a broader review of studies, both human and animal, that examine the role of cytokines in epilepsies. (Li et al. *supra,* at Ex. D.) Reviewing IL-1β, the authors explain that while animal models have supported the epileptic potential of IL-1β only at high doses, at least some human studies have had more mixed results, citing two studies that failed to detect elevated IL-1β following generalized tonic-clonic seizures, such as those at issue in this case. (*Id.* at p. 2.) Thus, consistent with Dr. Holmes's view, the authors indicate that while an association between IL-1β and seizures may exist, a distinct role of IL-1β in epilepsy has not been shown. (*Id*.)

Dr. Staats further explained that in the studies cited by Dr. Kinsbourne "the route of delivery is somewhat artificial when compared to vaccine-induced cytokine production." (Tr. 141.) For instance, Dr. Staats notes that the Dube study did not utilize vaccination nor demonstrate how cytokine-induced inflammation can cause seizure without fever. (Ex. H, p. 3.) Moreover, Dr. Staats opines that the Dube study is too far removed from the real-world context of vaccine-induced innate immune response to be informative. (Tr. 141-42; Ex. H, p. 3.) Both of respondent's experts stress that IL-1β was directly injected into the brains of the mice at a much higher dosage than would be expected following vaccination. (Tr. 141, 155; Ex. H, p. 3; Ex. E, p. 8; *see also* Ex. D, p. 2 (Dr. Holmes notes that the dosages were "1000X greater than those found in blood following vaccination in humans").) Ultimately, Dr. Kinsbourne agreed during the hearing that the Dube study involved higher levels of IL-1β than would be expected in a real world context.[26] (Tr. 61-62.)

Instead, Dr. Staats cites other studies contextualizing the degree to which IL-1β circulates in the blood after vaccination. Specifically, in a human trial where interleukin-1 alpha ("IL-1α")[27] was delivered intravenously over 6 hours at much higher doses than normally induced by peripheral activation of the innate immune system, fever developed at 2-6 hours of infusion and there were no reports of seizure activity. (Ex. E, p. 7 (citing Weisdorf et al., *supra,* at Ex. E, Tab 51).) In another human trial where IL-1α was

[26] Dr. Staats also offers competing animal studies that he suggests further undermine Dr. Kinsbourne's independent pathways theory. (Ex. H, pp. 2-3; Ex. E, pp. 4-8.) For example, he cites a mouse model that compared the effect of parenteral administration of the whole cell pertussis vaccine and acellular pertussis vaccination on IL-1β levels and seizure-like behavioral changes, finding that immunization with the acellular pertussis vaccine induced neither an elevation of IL-1β in the brain nor behavioral changes. (Ex. E, p. 6 (citing Donnelly et al., *supra,* at Ex. E, Tab 19).)

[27] Dr. Staats explained that IL-1α and IL-1β are forms of IL-1 that bind to the same receptors and have similar biological activity. (Tr. 138-39; Exs. E, p. 5; John W. Smith, et al., *The Effects of Treatment with Interleukin-1α on Platelet Recovery After High-Dose Carboplatin,* 328 NEW ENG. 756, 759 (Ex. E, Tab 53, p. 4).) Accordingly, studies concerning IL-1α are relevant at least to the extent that they concern the outcome of stimulation with IL-α and IL-1β. (Tr. 139.) In his work, Dr. Staats uses a recombinant IL-1 that is produced in a laboratory as a purified protein. (*Id.* at 138-39.)

administered by intravenous infusion for 5 days, several adverse effects were observed, including fever, but there was no mention of seizure. (*Id.* (citing John W. Smith, *The Effects of Treatment with Interleukin-1α on Platelet Recovery After High-Dose Carboplatin*, 328 NEW ENG. J. MED. 756 (1993) (Ex. E, Tab 53)).) In his own work, Dr. Staats has found that, even with direct application of IL-1 at concentrations not likely to be induced by vaccines and by routes that may allow IL-1 easier access to the central nervous system, there was no link between the use of IL-1 as a vaccine adjuvant and the induction of seizures. (*Id.* at 6-7.)

In any event, the specific purpose of the Dube study relied on heavily by Dr. Kinsbourne was to test "the hypothesis that endogenous IL-1β contributes to the mechanisms of *fever-induced seizures*, and that these IL-1β actions are independent of genetic background." (Dube et al., *supra,* at Ex. 48, p. 3 (emphasis added).) In that regard, the finding relied upon by Dr. Kinsbourne – that high doses of IL-1β could produce seizures without increased brain temperature – was not reported in isolation. It was one of three principle findings, along with findings relating to IL-1β signaling in the context of febrile seizures, that led the authors to "implicate IL-1β among the mechanisms by which fever provokes seizures in the developing brain." (*Id.* at 5.) Dr. Staats explains that Dube et al. used a model of direct injection of IL-1β into the brain that actually bypassed the fever control center of the brain, making it impossible to conclude that the study demonstrates that IL-1 can actually induce a seizure in the absence of fever. (Tr. 155.) Similarly, Vezzani & Baram indicated: "The mechanisms by which fever evokes febrile seizures are not fully elucidated, but a role for IL-1β is supported by several lines of evidence." (Vezzani & Baram, *supra,* at Ex. 22, p. 4.) However, the authors also observed that IL-1β "is not synthesized or released during other types of experimental seizures in the immature rodent." (*Id.*) On respondent's behalf, Dr. Staats interprets this observation as implying that afebrile seizures are not caused by inflammation as would be seen with febrile seizures following vaccination. (Ex. H, p. 2.)

Finally, even if Dr. Kinsbourne succeeded in demonstrating a theory by which S.H.'s first seizure could be considered vaccine-caused, he would still need to demonstrate that the first seizure resulted in epilepsy. In that regard, Dr. Holmes is also persuasive in rebutting Dr. Kinsbourne's theory that brief afebrile seizures of the type suffered by S.H. beget further seizures. (Tr. 97-100.) Where Dr. Kinsbourne has in the past been successful in presenting his theory that seizures beget seizures, the initiating seizures were complex febrile seizures.[28] *See, e.g.*, *Fuller*, 2019 WL 7576382, at *15-16. Here, however, there is no debate that S.H.'s seizures only lasted around 2-3

[28] As previously noted, rulings and decisions of other special masters are not binding. *See supra* note 21. Here, I note *Fuller* only to acknowledge the context in which Dr. Kinsbourne's theory has been otherwise accepted and to elucidate why the instant case presents a different scenario. In response to my inquiry into whether his prior cytokine-based theory in *Fuller* conflicts with his proposed theory in this case, Dr. Kinsbourne explained that his report in *Fuller* cited medical literature that was relevant to that case but that did not "tell the whole story." (Ex. 28, pp. 3-4.) He then clarified his separate pathway theory, which I have already explained is unpersuasive on this record. (*Id.*) However, the actual question presented in *Fuller* (*i.e.*, whether complex febrile seizures can lead to epilepsy) is not before me.

minutes. There is similarly no question that the events were not febrile.[29] Dr. Kinsbourne ultimately conceded in his testimony that S.H. suffered brief, generalized tonic-clonic seizures, despite previously opining in his expert report that she suffered complex seizures with focal features. (*Compare* Tr. 33, *with* Ex. 28, p.3.) Dr. Holmes likewise testified that, if seizures, S.H.'s events were more likely generalized tonic-clonic seizures than complex seizures. (Tr. 115.) In that context, though there is no dispute that seizures themselves produce some inflammation, Dr. Holmes explained that Dr. Kinsbourne's theory is a "huge stretch" of the cytokine literature (which itself does not involve vaccination) and not plausible. (*Id.* at 100, 103-04.)

Dr. Holmes explained that Dr. Kinsbourne's theory is a misapplication of the so called "kindling theory," which is itself no longer viewed favorably by the medical community. (Tr. 98-99.) While seizure activity can cause the brain to become more susceptible to seizures, it does not cause epilepsy resulting in spontaneous afebrile seizures. (*Id*.) According to Dr. Holmes, although epileptic seizures are related in the sense that they are all due to the same underlying cause, it is not the case that seizure A causes seizure B, etc. (*Id.* at 124-25.) He flatly denied that a three-minute seizure like those present in this case would produce a cytokine response that would explain any subsequent seizure, even one occurring shortly after the first event. (*Id.* at 99-100.) Even in the more serious condition of status epilepticus, which S.H. is "not even close to having," studies have shown anti-inflammatory treatments have not worked, casting doubt on any relationship to inflammation. (*Id.* at 99.)

For these reasons, I find that petitioner has not satisfied *Althen* prong one.

d. *Althen* Prong Two

The second *Althen* prong requires that petitioner demonstrate a logical sequence of cause and effect, which is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326-27 (Fed. Cir. 2006); *Grant*, 956 F.2d at 1148-49. The opinions and views of petitioner's treating physicians are entitled to some weight as treating physicians are in the best position to determine whether the subject vaccine was the reason for the alleged injury. *See* § 300aa-13(b); *Capizzano*, 440 F.3d at 1326. However, medical records and/or statements of treating physicians do not *per se* bind the special master to adopt such conclusions, even if they must be considered and carefully evaluated. *See* § 300aa-13(b)(1) ("Any . . . diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master . . . ."); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 745 n.67 (explaining that nothing "mandates that the testimony of a treating physician is sacrosanct—that is much be accepted in its entirety and cannot be rebutted").

[29] There was some suggestion in Dr. Kinsbourne's expert reports that S.H. could have had a fever that was either inhibited by a release of IL-1β or had gone undetected by her treating physicians because it was not a significant increase in temperature. (Exs. 28, p. 5 ("If fever is in evidence, it is very low grade."); Ex. 45, p. 4 ("A brief low-grade fever could easily be overlooked.").) At the hearing, Dr. Kinsbourne clarified that there was no documented fever preceding S.H.'s seizures. (Tr. 45, 60-61.) As such, any suggestion that S.H. may have had a low-grade fever is not supported by the record.

There is some indication in the records that S.H.'s treating physicians were willing to attribute S.H.'s initial seizure event to her preceding vaccinations. (Ex. 4, pp. 10, 12, 14.) However, while one of S.H.'s treating physicians, Dr. Marzo, reported the initial event to VAERS (Ex. 4, p. 14), S.H.'s neurologist, Dr. Sarco, specifically noted that the absence of fever was more concerning for epilepsy (Ex. 27, p. 71). Moreover, both of S.H.'s neurologists – Dr. Bose and Dr. Sarco – expressed doubt that the vaccine(s) caused S.H.'s seizures once they recurred. (Ex. 5, pp. 2-3, 42-43, 71-72, 229.) Accordingly, even crediting Dr. Marzo's VAERS report as some evidence pertaining to the cause of S.H.'s initial seizure, the treating physician opinions on the whole still do not meaningfully support Dr. Kinsbourne's opinion. Whereas Dr. Kinsbourne is explicit in opining that S.H.'s vaccinations caused not merely a single seizure event, but her epilepsy (*see* Ex. 24), Dr. Sarco in particular considered "immunization induced events" and "inherent mild epilepsy" to be alternative explanations. (Ex. 27, p. 71).

Respondent's experts also challenge the idea that Dr. Kinsbourne's theory could be operative in the context of S.H.'s own clinical history. Specifically, Dr. Holmes contends that, if Dr. Kinsbourne's theory were correct, then there would have to be some evidence of an ongoing cytokine-induced inflammatory process, such as a fever or some indication of inflammation in the MRI, EEG, spinal fluid examination, or clinical history. (Tr. 100-01; Ex. G, p. 2.) Dr. Staats suggested that, even if fever serves only as a proxy for detecting excessive inflammation, it would be impossible to posit excessive post-vaccination inflammation leading to seizure in the absence of such a proxy. (Tr. 138.) Dr. Kinsbourne's only response is to contend that S.H.'s presentation is explained by a low seizure threshold that resulted in rapid seizure onset, which in turn resulted in insufficient time for a clinically measurable fever to develop. (Ex. 45, p. 5-6.) Yet, Dr. Kinsbourne acknowledged that genetic testing confirmed that S.H. did not have any predisposition to seizures or epilepsy (Tr. 62) and he conceded having no basis for asserting that S.H. had any unusually low seizure threshold in the first place (*Id.* at 43-44). That is, Dr. Kinsbourne seeks to support his explanation of events by reference to a vulnerability – an unusually lowered seizure threshold – that he cannot substantiate based on any facts within S.H.'s own medical history.[30] In fact, when pressed during the hearing, Dr. Kinsbourne could not distinguish S.H.'s medical course from the typical course of childhood epilepsy, apart from what he indicates as coincident timing of vaccination. (*Id.* at 75.) Dr. Holmes explained that epilepsy is "pretty common" in children. (*Id.* at 94.) It is more common in children than adults, affecting up to about 1% of children. (*Id.*)

[30] Notably, Dr. Kinsbourne has been repeatedly criticized for employing circular logic when the facts fail to align with his theory. *See, e.g.*, *Holmes v. Sec'y of Health & Human Servs*., No. 08-185V, 2011 WL 2600612, at *14 (Fed Cl. Spec. Mstr. Apr. 26, 2011) (observing that "[t]o rely on the initial seizures themselves as evidence of a lowered seizure threshold would be circular reasoning" and rejecting Dr. Kinsbourne's opinion for seeking to rely on facts not supported by the medical records); *Dodd v. Sec'y of Health & Human Servs*., No. 09-0585V, 2013 WL 3233210, at *14 (Fed. Cl. Spec. Mstr. June 5, 2023) (explaining that "Dr. Kinsbourne's circular logic, that one event was caused by another simply because the second event occurred, is also unavailing"), *review denied*, 114 Fed. Cl. 43 (2013); *Gram ex rel. A.L.M.*, 2022 WL 17687972, at *46 (same).

Instead, Dr. Kinsbourne's opinion is based on his belief that there could be no other "feasible alternative cause" because so little time had passed between vaccination and onset of seizure activity. (Tr. 46-48.) But the Federal Circuit has explained that, "[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant*, 956 F.2d at 1149). That is, vaccines are not the cause of every unfortunate event that occurs soon after their administration. *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *9 (Fed. Cl. Spec. Mstr. July 16, 2004), ***aff'd***, 64 Fed. Cl. 19 (2005), ***aff'd***, 451 F.3d 1352 (Fed. Cir. 2006), *cert. denied*, 551 U.S. 1102 (2007). Here, I am not persuaded by Dr. Kinsbourne's mere *post hoc, ergo propter hoc* reasoning. In fact, for the reasons discussed under *Althen* prong three, the timing of S.H.'s seizures relative to vaccination more likely counsels *against* implicating S.H.'s vaccinations.

For these reasons, I find that petitioner has not satisfied *Althen* prong two.

e. *Althen* Prong Three

The third *Althen* prong requires "a showing of a proximate temporal relationship," or "medically-acceptable temporal relationship," between the vaccination and alleged injury. *Althen*, 418 F.3d at 1278, 1281. Petitioner must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan,* 539 F.3d at 1352. The explanation for what is a medically acceptable timeframe must coincide with *Althen* prong one, that is, with the theory of how the subject vaccine can cause the alleged injury. *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 105 Fed. Cl. 353, 360 (2012) (explaining that petitioner must first establish a medically acceptable timeframe to infer causation, *i.e.*, a medically acceptable timeframe in which symptoms would be expected to arise if the alleged injury was caused by the subject vaccine, and then, petitioner must show that the onset of the alleged injury occurred during that timeframe), ***aff'd***, 503 Fed. App'x 952 (Fed. Cir. 2013); *Williams v. Sec'y of Health & Human Servs.*, No. 17-255, 2023 WL 4401095, at *23 (Fed. Cl. Spec. Mstr. June 12, 2023).

The medical records reflect that S.H. was administered the vaccinations at issue in this case at about 9:50AM on May 22, 2015. (Ex. 3, p. 110.) When she first presented for care for her reported seizures, her parents reported the vaccines had been administered at about 9:30AM. (Ex. 6, p. 3.) The seizure occurred at about 10:30AM that same morning, at which time S.H. was taken directly to the emergency department. (*Id*.) She was first triaged at the emergency department at 11:10AM. (*Id*. at 10.) Accordingly, S.H.'s first seizure occurred an hour or less after her vaccination. Petitioner asserts that onset of S.H.'s afebrile seizures approximately one-hour post-vaccination is medically acceptable. (ECF. 81, pp. 20-21.) However, Dr. Kinsbourne provided no medical explanation to support that assertion. Based on epidemiology, he

opined that the risk window for post-vaccination seizures is generally considered to be within the first 24-72 hours, going so far as to say that it is "most often within a matter of hours," but he explained that the available epidemiology does not break down data hour by hour. (Tr. 48; Ex. 7, p. 4.) Accordingly, epidemiology does not answer this question.[31]

In contrast, Dr. Staats presented an opinion supported to at least some degree by medical literature that onset in this case was too rapid to be attributed to the vaccine based on the specifics of the theory Dr. Kinsbourne has proposed. (Ex. E, p. 7.) Specifically, Dr. Staats explained that post-vaccination cytokines generally peak 3 to 12 hours after vaccination. (Tr. 134.) Even in experimental animal models administering high doses of adjuvant, the first fevers manifest after two hours and measurable cytokines begin at about three hours. (*Id.* at 136-37.) Thus, Dr. Staats opines that vaccine-induced inflammation at the one-hour mark would not be robust enough to cause a seizure event, especially in the absence of fever. (*Id.* at 140.) Dr. Staats stressed that the two-hour post-vaccination events in experimental studies stem from an artificial direct administration of IL-1 whereas, in a true clinical setting, a seizure would be a downstream consequence of proinflammatory cytokines reaching the brain, meaning that a one-hour onset is simply not compatible with a cytokine response leading to an adverse event. (*Id.* at 144.)

Petitioner's counsel's cross examination raised an important limitation regarding several of the studies cited by Dr. Staats – namely, that they did not actually measure fever or cytokine response within one hour of inducing the response. (Tr. 146-50 (discussing Gwinn et al., *supra,* at Ex. E, Tab 45; Emmanuel Katsanis et al., *Infusions of Interleukin-1α After Autologous Transplantation for Hodgkin's Disease and Non-*

[31] Dr. Kinsbourne cites several pieces of medical literature that provide some support for his claim that onset of post-vaccination seizures can be between 24 and 72 hours after vaccination. (Ex. 7, p. 2, 4) (citing von Spiczak et al, *supra,* at Ex. 20; Sun et al., *supra,* at Ex. 21).) However, Dr. Holmes points out that the sole piece of medical literature that Dr. Kinsbourne provides to support his assertion that post-vaccination seizures can occur within less than 24 hours is not applicable in this case given that the study examined whole cell pertussis vaccination. (Ex. A, p. 13; Tr. 97 (discussing Murphy, Sarff, & Marquardt, *supra,* at Ex. 18.)) While Murphy et al. observed a minimum one-hour interval between immunization with the whole cell pertussis vaccine and onset of seizure activity among 22 subjects, the study had very significant limitations. First, the study was based on questionnaires sent to parents. There is no indication that the reported onset periods were confirmed in any way. Second, the authors stressed that the questionnaires were not sent to a random sample of families with vaccinated children. Instead, the authors sought out parents that already believed their child had suffered an adverse reaction. Third, no control group was utilized. Thus, the authors explain "[c]are must be taken to avoid overinterpretation of our data. There are inherent biases secondary to the method of collection . . . The long delay from the initial seizure to the report in many subjects, while permitting prolonged follow-up, did limit the accuracy of some of the collected data. The lack of control subjects make it difficult to ascribe a causal relationship to pertussis vaccine." (Murphy, Sarff, & Marquardt, *supra,* at Ex. 18, p. 4.) Moreover, the study's discussion is inadequate to characterize the specific subject that represented the minimum one-hour latency. Among the 22 study subjects, one was already ill with suspected whooping cough at the time of vaccination, one had tuberous sclerosis believed to explain the seizures, and two were siblings suspicious for a familial predisposition. Two of the subjects ultimately suffered infantile spasms.

Hodgkin's Lymphoma Induce Effector Cells with Antilymphoma Cytolytic Activity, 14 J. CLINICAL IMMUNOLOGY 205 (1994) (Ex. E, Tab 52); Smith, *supra,* at Ex. E, Tab 53).) Additionally, during cross-examination Dr. Staats acknowledged that anaphylaxis can produce systemic inflammation within less than an hour of vaccination. (*Id.* at 150-51.) However, on further questioning from the undersigned, Dr. Staats explained that cytokines are a category of molecule that encompasses many different proteins. Whereas Dr. Kinsbourne's theory relies on a specific cytokine in IL-1β, "vaccines may induce an array of proinflammatory cytokines" and "those proinflammatory cytokines may be something other than IL-1." (*Id.* at 153.) Dr. Staats explained that he has cited papers that show, "where it has been measured, IL-1 was not one of the cytokines that came up early." (*Id.* at 154-55 (discussing Valensi, Carlson, & Van Nest, *supra,* at Ex. E, Tab 1; Buglione-Corbett, *supra,* at Ex. E, Tab 43; Nakayama et al., *supra,* at Ex. E, Tab 44).)

In contrast, when asked directly if the onset in this case was "too soon after her vaccination" to infer causation, Dr. Kinsbourne indicated, "

> We have no way of rationalizing that. We don't know. . . . [T]here's nothing to tell us that it's going to happen after, say, two hours, after one hour. . . . [H]ow many hours something takes really we don't have knowledge of mechanism that exquisite. . . . I think it's perfectly possible as far as we know.

(*Id.* at 48.) This answer offers no attempt to meaningfully grapple with the timing issue and, even accounting for the limitations of the cited literature, Dr. Staats' competing testimony refutes this assertion that the issue cannot be rationalized or meaningfully explored based on the mechanism Dr. Kinsbourne himself proposed. Dr. Staats not only establishes that there is a body of literature touching on this issue, but that familiarly with that literature actually suggests reasons to conclude that the timing relied upon by Dr. Kinsbourne is suspect. During cross examination, Dr. Kinsbourne had a further exchange with respondent's counsel illuminating on this point:

> Q: And let's talk about the minimum time frame. You wrote in your first report and you testified here today that there's not really a minimal temporal interval stipulated based on the medical literature. Is that correct?
>
> A: I haven't seen anybody say it can't happen sooner than X.
>
> Q: And even as someone without experience in research in cytokines, we can agree that it takes time for the body to create proinflammatory cytokines in response to vaccination and that it would take time for them to [reach] the brain. Correct?
>
> A: Yes.

> Q: So, for example, if someone has a seizure 30 seconds after vaccination, that's not likely to be due to proinflammatory cytokines created in response to the vaccine. Is that correct?
>
> A: Well, it sounds correct. I haven't really thought about it, of course, but see, what – as I stated, if the seizure threshold is low, it can be tipped over very fast. Now, how fast, very fast is, I really can't say. But I don't see – I'm not aware of evidence that rules out one hour as being a sufficient interval. It's not something we can guess at.

(*Id.* at 66-67.)

Importantly, petitioner bears the burden of proof under *Althen* prong three and Dr. Kinsbourne's testimony effectively confirms she cannot meet that burden. The Federal Circuit has cautioned against setting "hard and fast" deadlines for onset. *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015). However, the Court of Federal Claims has also previously observed that while the *Althen* Court rejected the need for scientific certainty, "in 'a field bereft of complete and direct proof of how vaccines affect the human body,' . . . . [t]he standard of proof does not operate as a sliding scale that varies depending upon the quantity and quality of the scientific evidence that is available." *Caves v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 119, 143 (2011) (quoting *Althen*, 418 F.3d at 1280), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012). Here, the fact that Dr. Kinsbourne cannot locate medical literature *disproving* his opinion does not render it supported, especially where Dr. Kinsbourne's own testimony suggests he has not even thought the issue through himself.

On the whole, while Dr. Kinsbourne has disclaimed any need or ability to determine whether his own theory could unfold over the course of as little as one hour, Dr. Staats has provided a far more detailed presentation persuasively opining that it is less likely that it could, given the mechanisms actually underlying Dr. Kinsbourne's proposed theory. Accordingly, there is not preponderant evidence that it is medically reasonable to infer causation in this case based on Dr. Kinsbourne's proffered theory. Thus, I find that petitioner has not satisfied *Althen* prong three.

f. Weighing the Expert Testimony

Where both parties offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L.Ed.2d 508 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08–601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. Appx. 999

(Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Respondent asserts in his briefing that Dr. Kinsbourne's credentials do not include any specialized education, training, or expertise in pediatric immunology or seizure disorders and that he has no prior experience studying, or working with, cytokines or immune responses to vaccination and the potential effect on seizure threshold in children. (ECF No. 79, p. 13-15.) Respondent argues that, apart from his one year of pediatric residency in 1958-1959 and board certification in 1968, Dr. Kinsbourne's pediatric experience is limited to neuropsychology. (*Id.* at 13.) Respondent further stresses that the length of time since Dr. Kinsbourne has clinically treated a patient creates doubt about his qualification to opine on the medical issues in this case. (*Id.* at 14.) Due to lack of experience in pediatric immunology and seizure disorders, respondent submits that I should apply less weight to Dr. Kinsbourne's opinions when compared to Dr. Holmes, who is a practicing clinical pediatric neurologist with special interest in seizure disorders and epilepsy. (*Id.*)

Respondent's point is well taken. *See Bangerter ex rel. D.B.*, 2022 WL 439535, at *30. *But see Eilan ex rel. A.E. v. Sec'y of Health & Human Servs.*, No. 15-381V, 2021 WL 1085925, at *29-31 (Fed. Cl. Spec. Mstr. Feb. 23, 2021). Both Drs. Kinsbourne and Holmes have the requisite training in neurology to be accepted as experts. However, Dr. Holmes' clinical and research experience is more up-to-date and more relevant to the issues addressed. Dr. Holmes currently holds a position as Physician Leader in Neurology Health Care Service at Fletcher Allen Health Care in Burlington, Vermont, as well as positions as Professor and Chair of Neurological Sciences and Professor of Pediatrics at the University of Vermont College of Medicine. (Ex. B, p. 2.) Before that, his work focused specifically on childhood epilepsy, including, for instance, his role as Director of Pediatric Epilepsy Program at Talmadge Hospital in Augusta, Georgia, as well as his roles as Director of Clinical Neurophysiology Laboratory and Epilepsy Program and Director of the Center for Research in Pediatric Epilepsy at Children's Hospital in Boston, Massachusetts. (*See id.*) He has been on the editorial boards of several scientific journals focused on epilepsy and participated in countless lectures on the subject of epilepsy. (*See id.* at 6-7, 15-33.) He also written hundreds of peer-reviewed articles, abstracts, chapters, and books on the topic of epilepsy. (Tr. 82.)

On the other hand, Dr. Kinsbourne has not maintained a clinical practices since the early 1990s. (Tr. 56; Ex. 8, p. 2.) While he submits that he has continued to keep up with the field (Tr. 29), Dr. Holmes indicated that a clinical practice is essential to staying up-to-date in such an evolving field. (*Id.* at 80). Moreover, in his current positions, Dr. Kinsbourne teaches graduate students, not medical students, and he could not say for certain whether he has published, researched, or taught about seizure

disorders in the past 30 or so years. (*Id.* at 29, 56.) As for respondent's contention that Dr. Kinsbourne lacks sufficient experience in pediatric neurology, Dr. Kinsbourne held significant professorships in pediatric neurology toward the beginning of his career and testified to his specific training in pediatric neurology, albeit many decades ago. (*Id*. at 28-29; Ex. 8, p. 1-2.) Even so, a comparison of their respective curricula vitae reveals that Dr. Holmes has more clinical and research experience in childhood epilepsy specifically. While Dr. Kinsbourne was proffered to testify as an expert without objection, the length of time he has been out of active clinical practice and the differences between his and Dr. Holmes's experience are too extreme to go unmentioned. Dr. Holmes' opinion is clearly entitled to comparatively more weight.[32]

Additionally, in determining whether a particular expert's testimony was reliable or credible, a special master may consider whether the expert is offering an opinion that exceeds the expert's training or competence. *Walton v. Sec'y of Health & Human Servs.*, No. 04–503V, 2007 WL 1467307, at *17–18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). While all testimony of the experts offered at the entitlement hearing was heard and considered, a special master may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See*, *e.g., King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78–79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications).

It is also concerning that Dr. Kinsbourne's theory relating to cytokines relies so heavily on immunology when his opinion differs so much from respondent's expert, Dr. Staats, who has far more relevant expertise in immunology. (*See, e.g.*, Ex. 7, p. 3.) While neurologists must have some latitude to discuss immunologic causes of neurologic injuries, Dr. Kinsbourne is not an immunologist or a neuro-immunologist. Although Dr. Kinsbourne testified to the overlap between neurology and immunology (Tr. 55), he acknowledged having no professional training with respect to cytokines (*id.*), reducing his credibility on the very subject that forms the core of his theory. *Accord Bangerter ex rel. D.B.*, 2022 WL 439535, at *30 (recognizing that a special master's

[32] *Martin v. Sec'y of Health & Human Servs.,* No. 15-789V, 2020 WL 4197748, at *7, 31 (Fed. Cl. Spec. Mstr. May 8, 2020), *aff'd*, *Martin v. Sec'y of Health & Human Servs.*, No. 15-789V, slip op (Fed. Cl. 2020) ("Dr. Kinsbourne . . . has no demonstrated research or treatment expertise in the matters in dispute, and he relies on neurology expertise that has not been honed or refined, whether by clinical practice or research, for nearly 30 years."); *Jaafar v. Sec'y of Health & Human Servs.*, No. 15-267V, 2018 WL 4519066, at *3 (Fed. Cl. Spec. Mstr. Aug. 10, 2018) (concluding that petitioner did not establish DTaP vaccination caused infantile spasms and noting that "the most recent phase of [Dr. Kinsbourne's] career has had a shallower connection to pediatric neurology clinical care."); *Holmes*, 2011 WL 2600612 at *20 (questioning Dr. Kinsbourne's "clinical expertise in diagnosing and treating febrile seizures and epilepsy"); *Stone v. Sec'y of Health & Human Servs.*, No. 04-1041V, 2010 WL 1848220, at *8 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), *review granted, judgment rev'd sub nom*; *Stone v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 233 (2010) ("The fact that for the past twenty-five years Dr. Kinsbourne has not focused his practice, research or teachings in the field of seizure disorders, . . . significantly limited his ability to offer reliable, persuasive, and cogent testimony in this case."); *Hoskins v. Sec'y of Health & Human Servs.,* No. 15-071V, 2017 WL 3379270, at *5 (Fed. Cl. Spec. Mstr. July 12, 2017).

determination of an expert reliability may depend on "whether the expert is offering an opinion that exceeds the expert's training or competence"). I have in the past been critical of Dr. Kinsbourne for submitting expert opinions "beyond his areas of expertise and into the field of immunology." *Id.* Here, the difference in credentials between Dr. Staats and Dr. Kinsbourne is particularly germane to the above analysis under *Althen* prong three, where Dr. Kinsbourne effectively sought to equate the limitations of his own personal knowledge with the limits of the relevant science.

VI. Conclusion

There can be no doubt that what S.H. and her family experienced during her initial seizures and resulting treatment with anticonvulsants was frightening and stressful, and for that, they have my sympathy. However, for all of the reasons discussed above, I cannot conclude that S.H.'s seizures were vaccine-caused as there is not preponderant evidence that the subject vaccines could or did cause her condition. Therefore, I must conclude that petitioner is not entitled to compensation, and this case is **DISMISSED**.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master